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(54) Title: NF- $\kappa$ B INHIBITORS

(57) Abstract: The present invention provides novel compounds and methods for using them to treat diseases with aminothiophene inhibitors of IKK- $\beta$  phosphorylation of I $\kappa$ B. In so doing these aminothiophene inhibitors block pathological activation of transcription factor NF- $\kappa$ B in which diseases excessive activation of NF- $\kappa$ B is implicated.

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**NF- $\kappa$ B INHIBITORS****FIELD OF THE INVENTION**

This invention relates in general to a method of inhibiting pathological activation of the transcription factor NF- $\kappa$ B (nuclear factor- $\kappa$ B) using aminothiophene compounds. Such methods are particularly useful for treating diseases in which activation of NF- $\kappa$ B is implicated. More specifically, these methods may be used for inhibiting IKK- $\beta$  (I $\kappa$ B kinase- $\beta$ , also known as IKK-2) phosphorylation of I $\kappa$ B (inhibitory protein  $\kappa$ B)-which prevents subsequent degradation and activation of NF- $\kappa$ B dimers. Such methods are useful in the treatment of a variety of diseases associated with NF- $\kappa$ B activation including inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease) osteoarthritis; osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage; autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease, cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome, Ataxia Telangiectasia.

**BACKGROUND OF THE INVENTION**

Recent advances in scientific understanding of the mediators involved in acute and chronic inflammatory diseases and cancer have led to new strategies in the search for effective therapeutics. Traditional approaches include direct target intervention such as the use of specific antibodies, receptor antagonists, or enzyme inhibitors. Recent breakthroughs in the elucidation of regulatory mechanisms involved in the transcription and translation of a variety of mediators have led to increased interest in therapeutic approaches directed at the level of gene transcription.

Nuclear factor  $\kappa$ B (NF- $\kappa$ B) belongs to a family of closely related dimeric transcription factor complexes composed of various combinations of the Rel/NF- $\kappa$ B family of polypeptides. The family consists of five individual gene products in mammals, RelA (p65), NF- $\kappa$ B1 (p50/ p105), NF- $\kappa$ B2 (p49/ p100), c-Rel, and RelB, all of which can form hetero- or homodimers. These proteins share a highly homologous 300 amino acid "Rel homology domain" which contains the DNA binding and dimerization domains. At the extreme C-terminus of the Rel homology domain is a nuclear translocation sequence important in the transport of NF- $\kappa$ B from the cytoplasm to the nucleus. In addition, p65 and cRel possess potent transactivation domains at their C-terminal ends.

The activity of NF- $\kappa$ B is regulated by its interaction with a member of the inhibitor I $\kappa$ B family of proteins. This interaction effectively blocks the nuclear localization sequence on the NF- $\kappa$ B proteins, thus preventing migration of the dimer to the nucleus. A wide variety of stimuli activate NF- $\kappa$ B through what are likely to be multiple signal transduction pathways. Included are bacterial products (LPS), some viruses (HIV-1, HTLV-1), inflammatory cytokines (TNF $\alpha$ , IL-1), environmental and oxidative stress and DNA damaging agents. Apparently common to all stimuli however, is the phosphorylation and subsequent degradation of I $\kappa$ B. I $\kappa$ B is phosphorylated on two N-terminal serines by the recently identified I $\kappa$ B kinases (IKK- $\alpha$  and IKK- $\beta$ ). Site-directed mutagenesis studies indicate that these phosphorylations are critical for the subsequent activation of NF- $\kappa$ B in that once phosphorylated the protein is flagged for degradation via the ubiquitin-proteasome pathway. Free from I $\kappa$ B, the active NF- $\kappa$ B complexes are able to translocate to the nucleus where they bind in a selective manner to preferred gene-specific enhancer sequences. Included in the genes regulated by NF- $\kappa$ B are a number of cytokines and chemokines, cell adhesion molecules, acute phase proteins, immunoregulatory proteins, eicosanoid metabolizing enzymes and anti-apoptotic genes.

It is well-known that NF- $\kappa$ B plays a key role in the regulated expression of a large number of pro-inflammatory mediators including cytokines such as TNF, IL-1 $\beta$ , IL-6 and IL-8, cell adhesion molecules, such as ICAM and VCAM, and

inducible nitric oxide synthase (iNOS). Such mediators are known to play a role in the recruitment of leukocytes at sites of inflammation and in the case of iNOS, may lead to organ destruction in some inflammatory and autoimmune diseases.

The importance of NF- $\kappa$ B in inflammatory disorders is further strengthened by studies of airway inflammation including asthma, in which NF- $\kappa$ B has been shown to be activated. This activation may underlie the increased cytokine production and leukocyte infiltration characteristic of these disorders. In addition, inhaled steroids are known to reduce airway hyperresponsiveness and suppress the inflammatory response in asthmatic airways. In light of the recent findings with regard to glucocorticoid inhibition of NF- $\kappa$ B, one may speculate that these effects are mediated through an inhibition of NF- $\kappa$ B.

Further evidence for a role of NF- $\kappa$ B in inflammatory disorders comes from studies of rheumatoid synovium. Although NF- $\kappa$ B is normally present as an inactive cytoplasmic complex, recent immunohistochemical studies have indicated that NF- $\kappa$ B is present in the nuclei, and hence active, in the cells comprising rheumatoid synovium. Furthermore, NF- $\kappa$ B has been shown to be activated in human synovial cells in response to stimulation with TNF- $\alpha$  or IL-1 $\beta$ . Such a distribution may be the underlying mechanism for the increased cytokine and eicosanoid production characteristic of this tissue. See Roshak, A. K., et al., *J. Biol. Chem.*, **271**, 31496-31501 (1996). Expression of IKK- $\beta$  has been shown in synoviocytes of rheumatoid arthritis patients and gene transfer studies have demonstrated the central role of IKK- $\beta$  in stimulated inflammatory mediator production in these cells. See Aupperle et al. *J. Immunology* 1999. 163:427-433 and Aupperle et al. *J. Immunology* 2001;166:2705-11. More recently, the intra-articular administration of a wild type IKK- $\beta$  adenoviral construct was shown to cause paw swelling while intra-articular administration of dominant-negative IKK- $\beta$  inhibited adjuvant-induced arthritis in rat. See Tak et al. *Arthritis and Rheumatism* 2001; 44:1897-1907.

The NF- $\kappa$ B/Rel and I $\kappa$ B proteins are also likely to play a key role in neoplastic transformation and metastasis. Family members are associated with cell transformation *in vitro* and *in vivo* as a result of overexpression, gene amplification,



gene rearrangements or translocations. In addition, rearrangement and/or amplification of the genes encoding these proteins are seen in 20-25% of certain human lymphoid tumors. Further, NF- $\kappa$ B is activated by oncogenic ras, the most common defect in human tumors and blockade of NF- $\kappa$ B activation inhibits ras mediated cell transformation. In addition, a role for NF- $\kappa$ B in the regulation of apoptosis has been reported, strengthening the role of this transcription factor in the regulation of tumor cell proliferation. TNF, ionizing radiation and DNA damaging agents have all been shown to activate NF- $\kappa$ B which in turn leads to the upregulated expression of several anti-apoptotic proteins. Conversely, inhibition of NF- $\kappa$ B has been shown to enhance apoptotic-killing by these agents in several tumor cell types. As this likely represents a major mechanism of tumor cell resistance to chemotherapy, inhibitors of NF- $\kappa$ B activation may be useful chemotherapeutic agents as either single agents or adjunct therapy. Recent reports have implicated NF- $\kappa$ B as an inhibitor of skeletal cell differentiation as well as a regulator of cytokine-induced muscle wasting (Guttridge et al. *Science*; 2000; 289: 2363-2365.) further supporting the potential of NF- $\kappa$ B inhibitors as novel cancer therapies.

Several NF- $\kappa$ B inhibitors are described in C. Wahl, et al. *J. Clin. Invest.* 101(5), 1163-1174 (1998), R. W. Sullivan, et al. *J. Med. Chem.* 41, 413-419 (1998), J. W. Pierce, et al. *J. Biol. Chem.* 272, 21096-21103 (1997)

The marine natural product hymenialdisine is known to inhibit NF- $\kappa$ B. Roshak, A., et al., *JPET*, **283**, 955-961 (1997). Breton, J. J and Chabot-Fletcher, M. C., *JPET*, **282**, 459-466 (1997).

Additionally, patent applications have been filed on aminothiophene inhibitors of the IKK-2, see Callahan, et al., WO 2002030353; Baxter, et al., WO 2001058890, Faull, et al., WO 2003010158; Griffiths, et al., WO2003010163; Fancelli, et al., WO 200198290; imidazole inhibitors of IKK-2, see Callahan, et al., WO 200230423; anilinophenylpyrimidine inhibitors of IKK-2, see Kois, et al., WO 2002046171;  $\beta$ -carboline inhibitors of IKK-2, see Ritzeler, et al., WO 2001068648, Ritzeler, et al., EP 1134221; Nielsch, et al. DE 19807993; Ritzeler, et al., EP 1209158; indole inhibitors of IKK-2, see Ritzeler, et al., WO 2001030774;

- benzimidazole inhibitors of the IKK-2, see Ritzeler, et al., DE 19928424; Ritzeler et al, WO 2001000610; aminopyridine inhibitors of IKK-2, see Lowinger, et al, WO2002024679; Murata, et al, WO 2002024693; Murata, et al., WO2002044153; pyrazolaquinazoline inhibitors of IKK-2, see Beaulieu, et al.,
- 5 WO2002028860; Burke et al, WO2002060386, Burke, et al. US 20030022898; quinoline inhibitors of IKK-2, Browner, et al., WO2002041843, Browner, et al., US 20020161004 and pyridylcyanoguanidine inhibitors of IKK-2, see Bjorkling, et al., WO 2002094813, Binderup et al, WO 2002094322 and Madsen, et al., WO 200294265. The natural products staurosporine, quercetin, K252a and K252b have
- 10 been shown to be IKK-2 inhibitors, see Peet, G. W. and Li, J. J. *Biol. Chem.*, 274, 32655-32661 (1999) and Wisniewski, D., et al., *Analytical Biochem.* 274, 220-228 (1999). Synthetic inhibitors of IKK-2 have also been described, see Burke, et al. *J. Biol. Chem.*, 278, 1450-1456 (2003) and Murata, et al., *Bioorg. Med. Chem. Lett.*, 13, 913-198 (2003) have described IKK-2 inhibitors.
- 15 U.S. Patent No. 3,963,750 describes the preparation of certain aminothiophenes.

### **SUMMARY OF THE INVENTION**

The present invention involves novel compounds and novel methods of

20 inhibiting the activation transcription factor NF- $\kappa$ B using the present compounds.

An object of the present invention is to provide a method for treating diseases which may be therapeutically modified by altering the activity of transcription factor NF- $\kappa$ B.

Accordingly, in the first aspect, this invention provides a pharmaceutical

25 composition comprising a compound according to Formula I.

In another aspect, this invention provides a method of treating diseases in which the disease pathology may be therapeutically modified by inhibiting phosphorylation and subsequent degradation of I $\kappa$ B by IKK- $\beta$ .

In still another aspect, this invention provides a method of treating diseases

30 in which the disease pathology may be therapeutically modified by inhibiting pathological activation of NF- $\kappa$ B.

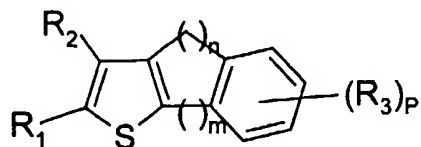
In a particular aspect, this invention provides methods for treating a variety of diseases associated with NF- $\kappa$ B activation including inflammatory and tissue repair disorders, particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease) osteoarthritis, 5 osteoporosis and fibrotic diseases, dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage; autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease, 10 cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome and Ataxia Telangiectasia.

**DETAILED DESCRIPTION OF THE INVENTION**

The compounds of the present invention are selected from Formula

(I) herein below:

5



(I)

wherein:

10 R<sub>1</sub> represents NR<sub>4</sub>R<sub>5</sub>;

R<sub>2</sub> represents CONH<sub>2</sub> or SO<sub>2</sub>NH<sub>2</sub>;

R<sub>3</sub> is selected from the group consisting of halogen, C<sub>1-4</sub>alkyl, NH<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, O-alkyl, S-alkyl, CN, CHO, SO<sub>2</sub>-alkyl, (CH<sub>2</sub>)<sub>q</sub>NR<sub>7</sub>R<sub>8</sub>, O-(CH<sub>2</sub>)<sub>q</sub>NR<sub>7</sub>R<sub>8</sub>, (CH<sub>2</sub>)<sub>q</sub>-aryl, O-(CH<sub>2</sub>)<sub>q</sub>-aryl, (CH<sub>2</sub>)<sub>q</sub>-heteroaryl, O-(CH<sub>2</sub>)<sub>q</sub>-heteroaryl, (CH<sub>2</sub>)<sub>q</sub>-heteroalkyl,

15 O-(CH<sub>2</sub>)<sub>q</sub>-heteroalkyl and NO<sub>2</sub>;

R<sub>4</sub> represents H or C<sub>1-4</sub>alkyl;

R<sub>5</sub> represents H or CONHR<sub>6</sub>;

R<sub>6</sub> is selected from the group consisting of hydrogen, alkyl and aryl;

R<sub>7</sub> represents C<sub>1-4</sub>alkyl;

20 R<sub>8</sub> represents C<sub>1-4</sub>alkyl;

m is 0, 1, 2 or 3;

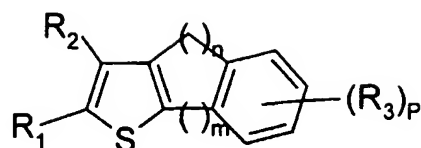
n is 0, 1, 2, or 3;

p is 1, 2 or 3; and

q is 1, 2, 3 or 4; or a pharmaceutically acceptable salt thereof.

25

Preferred:



( Ia )

wherein:

5 R<sub>1</sub> represents NR<sub>4</sub>R<sub>5</sub>;

R<sub>2</sub> represents CONH<sub>2</sub>;

R<sub>3</sub> is selected from the group consisting of halogen, C<sub>1-4</sub>alkyl, NH<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, O-alkyl, S-alkyl, CN, CHO, SO<sub>2</sub>-alkyl, (CH<sub>2</sub>)<sub>q</sub>NR<sub>7</sub>R<sub>8</sub>, O-(CH<sub>2</sub>)<sub>q</sub>NR<sub>7</sub>R<sub>8</sub>, (CH<sub>2</sub>)<sub>q</sub>-aryl, O-(CH<sub>2</sub>)<sub>q</sub>-aryl, (CH<sub>2</sub>)<sub>q</sub>-heteroaryl, O-(CH<sub>2</sub>)<sub>q</sub>-heteroaryl, (CH<sub>2</sub>)<sub>q</sub>-heteroalkyl,

10 O-(CH<sub>2</sub>)<sub>q</sub>-heteroalkyl and NO<sub>2</sub>;

R<sub>4</sub> represents H;

R<sub>5</sub> represents CONHR<sub>6</sub>;

R<sub>6</sub> represents H;

R<sub>7</sub> represents C<sub>1-4</sub>alkyl;

15 R<sub>8</sub> represents C<sub>1-4</sub>alkyl;

m is 0;

n is 1 or 2;

p is 1, or 2; and

q is 1, 2, 3 or 4; or a pharmaceutically acceptable salt thereof.

20 The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds, which release the active parent, drug according to Formula I *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and

25 diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have

unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

This invention provides methods for treating a variety of diseases associated with NF- $\kappa$ B activation including inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease) osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage; autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease, cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome, and Ataxia Telangiectasia.

Preferred compounds useful in the present invention include:

- 2-Amino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide;
- 2-Ureido-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide;
- 20 2-Acetylamino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide;
- 2-Amino-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;
- 2-Acetylamino-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;
- 2-Ureido-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;
- 2-Amino-8-methoxy-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide ;
- 25 8-Methoxy-2-ureido-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;
- 2-Amino-7-methoxy-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;
- 2-Acetylamino-7-methoxy-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;
- 2-Amino-7-bromo-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;

2-Acetylamino-7-bromo-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide; and 7-Bromo-2-ureido-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide; or a pharmaceutially acceptable salt thereof.

The meaning of any substituent at any one occurrence in Formula I or any  
5 subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

As used herein, "alkyl" refers to an optionally substituted hydrocarbon group joined by single carbon-carbon bonds and having 1-6 carbon atoms joined together. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or  
10 unsaturated. Substituents on optionally substituted alkyl are selected from the group consisting of aryl, OH, O-alkyl, CO, halogen, CF<sub>3</sub>, and OCF<sub>3</sub>.

As used herein, "aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. Aryl includes carbocyclic aryl, and biaryl groups,  
15 all of which may be optionally substituted. Substituents are selected from the group consisting of halogen, C<sub>1-4</sub> alkyl, NH<sub>2</sub>, OCF<sub>3</sub>, CF<sub>3</sub>, O-alkyl, S-alkyl, CN, CHO, SO<sub>2</sub>-alkyl and NO<sub>2</sub>.

As used herein, "heteroaryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to  
20 two conjugated or fused ring systems and 1-3 heteroatoms selected from O, S and N. Heteroaryl includes carbocyclic heteroarylaryl, aryl-heteroaryl and biheteroarylaryl groups, all of which may be optionally substituted. Preferred aryl include phenyl and naphthyl. More preferred aryl include phenyl. Preferred substituents are selected from the group consisting of halogen, C<sub>1-4</sub> alkyl, NH<sub>2</sub>, OCF<sub>3</sub>, CF<sub>3</sub>, O-alkyl, S-  
25 alkyl, CN, CHO, SO<sub>2</sub>-alkyl and NO<sub>2</sub>. Examples of heteroaryl rings included pyrrole, furan, thiophene, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, pyridine, quinoline, isoquinoline, quinolizine, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, pyridazine, pyrimidine, and pyrazine.

As used herein, "heteroalkyl" refers to an optionally substituted ring not  
30 having conjugated pi electron system containing up 1-3 heteroatoms selected from

O, S and N. Examples of heteroalkyl rings are piperidine, piperazine, morpholine, tetrahydrofuran, tetrahydropyran, and tetrahydrothiophene.

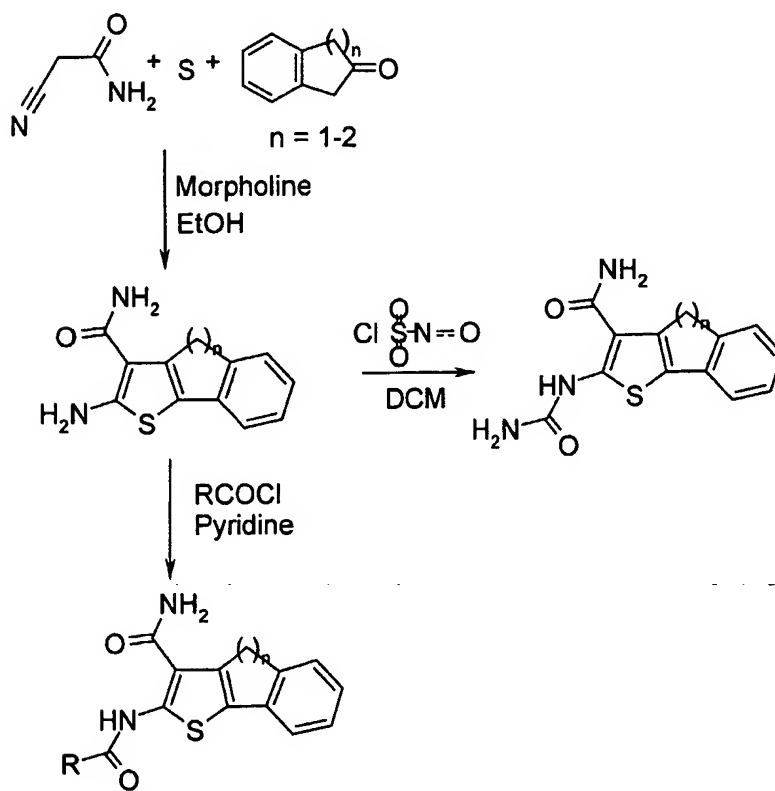
As used herein "halogen" refers to include F, Cl, Br, and I.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The general preparation of the aminothiophene analogs is shown in Schemes 1 and 2.

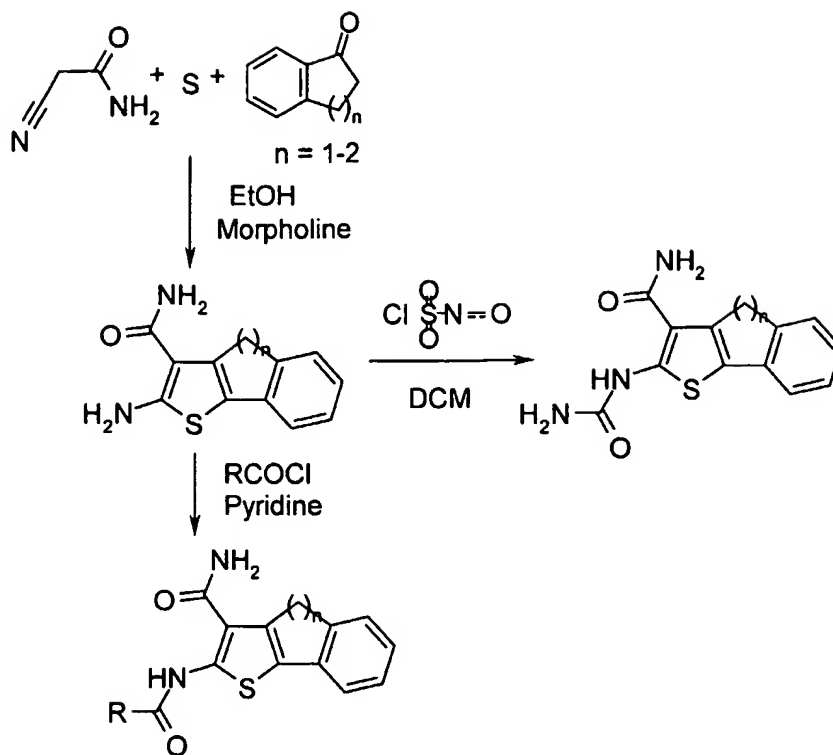
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### Scheme 1



15



**Scheme 2**

- 5 Morpholine is added to a stirred solution of cyanoacetamide, sulfur, and cyclic ketone in absolute ethanol. The resulting solution is stirred at room temperature or up to 60°C overnight. The solvent is then removed under *vacuo* and the residue is taken up into ethyl acetate, washed by water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under *vacuo* to give a dark
- 10 brown solid. The product is then usually purified by chromatography to give the desired product.

- This invention provides a pharmaceutical composition, which comprises a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient. Accordingly, the compounds of Formula I may be used in the
- 15 manufacture of a medicament. Pharmaceutical compositions of the compounds of Formula I prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to

use. The liquid formulation may be a buffered, isotonic, aqueous solution.

Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

Typical compositions for inhalation are in the form of a dry powder, solution, suspension or emulsion. Administration may for example be by dry powder inhaler (such as unit dose or multi-dose inhaler, e.g. as described in US Patent 5590645 or by nebulisation or in the form of a pressurized aerosol. Dry powder compositions typically employ a carrier such as lactose, trehalose or starch. Compositions for nebulisation typically employ water as vehicle. Pressurized aerosols typically employ a propellant such as dichlorodifluoromethane, trichlorofluoromethane or, more preferably, 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or

mixtures thereof. Pressurized aerosol formulations may be in the form of a solution (perhaps employing a solubilising agent such as ethanol) or a suspension which may be excipient free or employ excipients including surfactants and/or co-solvents (e.g. ethanol). In dry powder compositions and suspension aerosol compositions the  
5 active ingredient will preferably be of a size suitable for inhalation (typically having mass median diameter (MMD) less than 20 microns e.g. 1-10 especially 1-5 microns). Size reduction of the active ingredient may be necessary e.g. by micronisation.

Pressurized aerosol compositions will generally be filled into canisters fitted  
10 with a valve, especially a metering valve. Canisters may optionally be coated with a plastics material e.g. a fluorocarbon polymer as described in WO96/32150. Canisters will be fitted into an actuator adapted for buccal delivery.

Typical compositions for nasal delivery include those mentioned above for inhalation and further include non-pressurized compositions in the form of a solution  
15 or suspension in an inert vehicle such as water optionally in combination with conventional excipients such as buffers, anti-microbials, tonicity modifying agents and viscosity modifying agents which may be administered by nasal pump.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene  
20 glycols and molded into a suppository.

The methods of the present invention include topical, inhaled and intracolonic administration of the compounds of Formula I. By topical administration is meant non-systemic administration, including the application of a compound of the invention externally to the epidermis, to the buccal cavity and  
25 instillation of such a compound into the ear, eye and nose, wherein the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration. The amount of a compound of the invention (hereinafter referred to as the active ingredient) required for therapeutic or prophylactic effect upon topical administration will, of course,  
30 vary with the compound chosen, the nature and severity of the condition being

treated and the animal undergoing treatment, and is ultimately at the discretion of the physician

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.01 to 5.0 wt% of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carriers therefor and optionally any other therapeutic ingredients. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of where treatment is required such as: liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container, which is then sealed and sterilized by autoclaving, or maintaining at 90-100 C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may

also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

5 Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic  
10 soap, a mucilage, an oil of natural origin such as almond, corn, arachis, castor or olive oil, wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogols. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surface active agent such as sorbitan esters or polyoxyethylene derivatives  
15 thereof. Suspending agents such as natural gums, cellulose derivatives or in organic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

The compounds of Formula I are useful as inhibitors of the IKK-beta kinase phosphorylation of I $\kappa$ B and as such are inhibitors of NF- $\kappa$ B activation. The present  
20 method utilizes compositions and formulations of said compounds, including pharmaceutical compositions and formulations of said compounds.

The present invention particularly provides methods of treatment of diseases associated with inappropriate NF- $\kappa$ B activation, which methods comprise administering to an animal, particularly a mammal, most particularly a human in  
25 need thereof one or more compounds of Formula I. The present invention particularly provides methods for treating inflammatory and tissue repair disorders, particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease) osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation  
30 (UV)-induced skin damage, autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and

organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease, cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome and Ataxia

5 Telangiectasia.

For acute therapy, parenteral administration of one or more compounds of Formula I is useful. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the  
10 parenteral dose will be about 0.01 to about 50 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit IKK-beta and therefore activation of NF- $\kappa$ B. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 80 mg/kg/day. The precise amount of a compound used  
15 in the present method which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds of Formula I may also be administered orally to the patient,  
20 in a manner such that the concentration of drug is sufficient to inhibit IKK-beta and therefore activation of NF- $\kappa$ B or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about  
25 0.5 to about 20 mg/kg.

The compounds of Formula I may also be administered topically to the patient, in a manner such that the concentration of drug is sufficient to inhibit IKK-beta and therefore activation of NF- $\kappa$ B or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the  
30 compound is administered in a topical formulation of between about 0.01% to about 5% w/w.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The ability of the compounds described herein to inhibit the activation of NF- $\kappa$ B is clearly evidenced in their ability to inhibit the phosphorylation of the N-terminal fragment of I $\kappa$ B- $\alpha$  by IKK- $\beta$  (see Table 1 for examples). These compounds also block the degradation of I $\kappa$ B- $\alpha$  and the nuclear translocation of NF- $\kappa$ B in human monocytes and other mammalian cells upon activation of the cells with a pro-inflammatory stimuli (e.g., TNF- $\alpha$ , LPS, etc.). In addition these compounds inhibit pro-inflammatory mediator production from LPS-stimulated human monocytes and stimulated human primary synovial fibroblasts. The utility of the present NF- $\kappa$ B inhibitors in the therapy of diseases is premised on the importance of NF- $\kappa$ B activation in a variety of diseases.

NF- $\kappa$ B plays a key role in the regulated expression of a large number of pro-inflammatory mediators including cytokines such as TNF, IL-1 $\beta$ , IL-6 and IL-8 (Mukaida *et al.*, 1990; Liberman and Baltimore, 1990; Matsusaka *et al.*, 1993), cell adhesion molecules, such as ICAM and VCAM (Marui *et al.*, 1993; Kawai *et al.*, 1995; Ledebur and Parks, 1995), and inducible nitric oxide synthase (iNOS) (Xie *et al.*, 1994; Adcock *et al.*, 1994). (Full reference citations are at the end of this section). Such mediators are known to play a role in the recruitment of leukocytes at sites of inflammation and in the case of iNOS, may lead to organ destruction in some inflammatory and autoimmune diseases (McCartney-Francis *et al.*, 1993; Kleemann *et al.*, 1993).

Evidence for an important role of NF- $\kappa$ B in inflammatory disorders is obtained in studies of asthmatic patients. Bronchial biopsies taken from mild atopic asthmatics show significant increases in the number of cells in the submucosa staining for activated NF- $\kappa$ B, total NF- $\kappa$ B, and NF- $\kappa$ B-regulated cytokines such as GM-CSF and TNF $\alpha$  compared to biopsies from normal non-atopic controls (Wilson *et al.*, 1998). Furthermore, the percentage of vessels expressing NF- $\kappa$ B immunoreactivity is increased as is IL-8 immunoreactivity in the epithelium of the biopsy specimens (Wilson *et al.*, 1998). As such, inhibition of IL-8 production

through the inhibition of NF- $\kappa$ B, as has been demonstrated by these compounds would be predicted be beneficial in airway inflammation.

Recent studies suggest that NF- $\kappa$ B may also play a critical role in the pathogenesis of inflammatory bowel disease (IBD). Activated NF- $\kappa$ B is seen in  
5 colonic biopsy specimens from Chron's disease and ulcerative colitis patients (Ardite *et al.*, 1998; Rogler *et al.*, 1998; Schreiber *et al.*, 1998). Activation is evident in the inflamed mucosa but not in uninflamed mucosa (Ardite *et al.*, 1998; Rogler *et al.*, 1998) and is associated with increased IL-8 mRNA expression in the same sites (Ardite *et al.*, 1998). Furthermore, corticosteroid treatment strongly inhibits  
10 intestinal NF- $\kappa$ B activation and reduces colonic inflammation (Ardite *et al.*, 1998; Schreiber *et al.*, 1998). Again, inhibition of IL-8 production through the inhibition of NF- $\kappa$ B, as has been demonstrated by these compounds would be predicted be beneficial in inflammatory bowel disease.

Animal models of gastrointestinal inflammation provide further support for  
15 NF- $\kappa$ B as a key regulator of colonic inflammation. Increased NF- $\kappa$ B activity is observed in the lamina propria macrophages in 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice with p65 being a major component of the activated complexes (Neurath *et al.*, 1996; Neurath and Pettersson, 1997). Local  
administration of p65 antisense abrogates the signs of established colitis in the  
20 treated animals with no signs of toxicity (Neurath *et al.*, 1996; Neurath and Pettersson, 1997). As such, one would predict that small molecule inhibitors of NF- $\kappa$ B would be useful in the treatment of IBD.

Further evidence for a role of NF- $\kappa$ B in inflammatory disorders comes from studies of rheumatoid synovium. Although NF- $\kappa$ B is normally present as an inactive  
25 cytoplasmic complex, recent immunohistochemical studies have indicated that NF- $\kappa$ B is present in the nuclei, and hence active, in the cells comprising human rheumatoid synovium (Handel *et al.*, 1995; Marok *et al.*, 1996; Sioud *et al.*, 1998) and in animal models of the disease (Tsao *et al.*, 1997). The staining is associated with type A synoviocytes and vascular endothelium (Marok *et al.*, 1996).  
30 Furthermore, constitutive activation of NF- $\kappa$ B is seen in cultured synoviocytes



(Roshak *et al.*, 1996; Miyazawa *et al.*, 1998) and in synovial cell cultures stimulated with IL-1 $\beta$  or TNF $\alpha$  (Roshak *et al.*, 1996; Fujisawa *et al.*, 1996; Roshak *et al.*, 1997). Thus, the activation of NF- $\kappa$ B may underlie the increased cytokine production and leukocyte infiltration characteristic of inflamed synovium. The ability of these compounds to inhibit NF- $\kappa$ B and thereby inhibit the production of pro-inflammatory mediators (e.g. cytokines and prostanoids) by these cells would be predicted to yield benefit in rheumatoid arthritis.

#### **Biological Assays:**

The compounds of this invention may be tested in one of several biological assays to determine the concentration of compound, which is required to have a given pharmacological effect.

NF- $\kappa$ B activity may also be measured in an electrophoretic mobility shift assay (EMSA) to assess the presence of NF- $\kappa$ B protein in the nucleus. The cells of interest are cultured to a density of  $1 \times 10^6$  /mL. The cells are harvested by centrifugation, washed in PBS without Ca $^{2+}$  and Mg $^{2+}$  and resuspended in PBS with Ca $^{2+}$  and Mg $^{2+}$  at  $1 \times 10^7$  cells/mL. To examine the effect of compound on the activation of NF- $\kappa$ B, the cell suspensions are treated with various concentrations of drug or vehicle (DMSO, 0.1%) for 30 min. at 37 °C prior to stimulation with TNF- $\alpha$  (5.0 ng/mL) for an additional 15 min. Cellular and nuclear extracts are prepared follows. Briefly, at the end of the incubation period the cells ( $1 \times 10^7$  cells) are washed 2x in PBS without Ca $^{2+}$  and Mg $^{2+}$ . The resulting cell pellets are resuspended in 20 uL of Buffer A (10 mM Hepes (pH 7.9), 10 mM KCl, 1.5 mM MgCl $_2$ , 0.5 mM dithiothreitol (DTT) and 0.1% NP-40) and incubated on ice for 10 min. The nuclei are pelleted by microcentrifugation at 3500 rpm for 10 min at 4 °C. The resulting supernatant was collected as the cellular extract and the nuclear pellet was resuspended in 15 uL Buffer C (20 mM Hepes (pH 7.9), 0.42 M NaCl, 1.5mM MgCl $_2$ , 25% glycerol, 0.2 mM EDTA, 0.5 mM DTT, and 0.5 mM phenylmethylsulphonyl fluoride (PMSF)). The suspensions are mixed gently for 20 min at 4 °C then microcentrifuged at 14,000 rpm for 10 min at 4 °C. The supernatant is collected and diluted to 60 uL with Buffer D (20mM Hepes (pH 7.9),

50 mM KCl, 20% glycerol, 0.2 mM EDTA, 0.5 mM DTT, and 0.5 mM PMSF). All samples are stored at  $-80^{\circ}\text{C}$  until analyzed. The protein concentration of the extracts is determined according to the method of Bradford (Bradford, 1976) with BioRad reagents.

5        The effect of compounds on transcription factor activation is assessed in an electrophoretic mobility shift assay (EMSA) using nuclear extracts from treated cells as described above. The double stranded NF- $\kappa$ B consensus oligonucleotides (5'-AGTTGAGGGGACTTTCCCAGGC-3') are labelled with  $T_4$  polynucleotide kinase and [ $g$ - $^{32}\text{P}$ ]ATP. The binding mixture (25  $\mu\text{L}$ ) contains 10 mM Hepes-NaOH (pH 7.9), 4 mM Tris-HCl (pH 7.9), 60 mM KCl, 1 mM EDTA, 1 mM dithiothreitol, 10% glycerol, 0.3 mg/mL bovine serum albumin, and 1  $\mu\text{g}$  poly(dI-dC)•poly(dI-dC). The binding mixtures (10  $\mu\text{g}$  nuclear extract protein) are incubated for 20 min at room temperature with 0.5 ng of  $^{32}\text{P}$ -labelled oligonucleotide (50,000-100,000 cpm) in the presence or absence of unlabeled competitor after which the mixture is loaded on a 15    4% polyacrylamide gel prepared in 1X Tris borate/EDTA and electrophoresed at 200 V for 2 h. Following electrophoresis the gels are dried and exposed to film for detection of the binding reaction.

      The effect of compounds on the phosphorylation of I $\kappa$ B may be monitored in a Western blot. Cellular extracts are subjected to sodium dodecyl sulfate-20    polyacrylamide gel electrophoresis (SDS-PAGE) on 10% gels (BioRad, Hercules, CA) and the proteins transferred to nitrocellulose sheets (Hybond<sup>tm</sup>-ECL, Amersham Corp., Arlington Heights, IL). Immunoblot assays are performed using a polyclonal rabbit antibody directed against I $\kappa$ B $\alpha$  or I $\kappa$ B $\beta$  followed with a peroxidase-conjugated donkey anti-rabbit secondary antibody (Amersham Corp., Arlington Heights, IL). Immunoreactive bands are detected using the Enhanced Chemiluminescence (ECL) assay system (Amersham Corp., Arlington Heights, IL).

      Assays for I $\kappa$ B kinases were conducted as follows: IKK- $\alpha$  was expressed as a hexa-histidine tagged protein in baculovirus-infected insect cells and purified over a Ni-NTA affinity column. Kinase activity was assayed using 50 ng of purified 30    protein in assay buffer (20 mM Hepes, pH 7.7, 2 mM  $\text{MgCl}_2$ , 1 mM  $\text{MnCl}_2$ , 10 mM  $\beta$ -glycerophosphate, 10 mM NaF, 10 mM PNPP, 0.3 mM  $\text{Na}_3\text{VO}_4$ , 1 mM

benzamidine, 2  $\mu$ M PMSF, 10  $\mu$ g/ml aprotinin, 1  $\mu$ g/mL leupeptin, 1  $\mu$ g/mL pepstatin, 1mM DTT) containing various concentrations of compound or DMSO vehicle and ATP as indicated (Pharmacia Biotech Inc., Piscataway, NJ). The reaction was started by the addition of 200 ng I $\kappa$ B-GST (Santa Cruz Biotechnology, Inc., Santa Cruz, CA), in a total volume of 50  $\mu$ L. The reaction was allowed to proceed for 1 h. at 30  $^{\circ}$ C after which the reaction was terminated by the addition of EDTA to a final concentration of 20 mM. Kinase activity was determined by dissociation-enhanced lanthanide fluorescence immunoassay (Wallac Oy, Turku, Finland) using a phospho-I $\kappa$ B- $\alpha$  (Ser32) antibody (New England Biolabs, Inc., Beverly, MA) and an Eu<sup>3+</sup>-labelled anti-rabbit IgG (Wallac Oy, Turku, Finland). The plates were read in a VICTOR 1420 Multilabel Counter (Wallac), using a standard europium protocol (excitation 340 nm, emission 615 nm; fluorescence measured for 400  $\mu$ s after a 400 usec delay). Data are expressed as fluorescence (cps) units.

IKK- $\beta$  was expressed as a GST-tagged protein, and its activity was assessed in a 96-well scintillation proximity assay (SPA). Briefly, IKK- $\beta$  was diluted in assay buffer as described above (20 nM final), with various concentrations of compound or DMSO vehicle, 240 nM ATP and 200 nCi [ $\gamma$ -<sup>33</sup>P]-ATP (10 mCi/mL, 2000 Ci/mmol; NEN Life Science Products, Boston, MA). The reaction was started with the addition of a biotinylated peptide comprising amino acids 15 – 46 of I $\kappa$ B- $\alpha$  (American Peptide) to a final concentration of 2.4  $\mu$ M, in a total volume of 50  $\mu$ L. The sample incubated for one hour at 30  $^{\circ}$ C, followed by the addition of 150  $\mu$ L of stop buffer (PBS w/o Ca<sup>2+</sup>, Mg<sup>2+</sup>, 0.1% Triton X-100 (v/v), 10 mM EDTA) containing 0.2 mg streptavidin-coated SPA PVT beads (Amersham Pharmacia Biotech, Piscataway, NJ). The sample was mixed, incubated for 10 min. at room temperature, centrifuged (1000  $\times$ g, 2 minutes), and measured on a Hewlett-Packard TopCount.

In addition, IKK- $\beta$  or IKK- $\alpha$  activity is measured by phosphorylation of recombinant GST-I $\kappa$ B- $\alpha$  using time-resolved fluorescence resonance energy transfer (TR-FRET) in 384-well microtitre plates. Briefly IKK- $\beta$  or IKK- $\alpha$  is diluted

in assay buffer (50 mM HEPES pH 7.4 containing 10 mM magnesium chloride, 1 mM CHAPS, 1 mM DTT and 0.01% w/v BSA) to 5 nM final concentration. This is added to various concentrations of compound or DMSO vehicle and the reaction started by addition of 25 nM GST-IkappaBalpha and 1  $\mu$ M ATP in assay buffer to a  
5 volume of 30  $\mu$ L. After incubation for 30 min at ambient temperature the reaction was stopped by addition of 50 mM pH 7.4 EDTA (15  $\mu$ L). Detection of phosphorylated product was achieved by addition of a LANCE europium chelate labelled specific anti-phosphoserine monoclonal antibody at 0.5 nM final concentration (Cell signalling Technology via Perkin Elmer) and allophycocyanin  
10 labelled anti-GST antibody at 10 nM final concentration (Prozyme) to give a final volume of 60  $\mu$ L. After a further incubation at ambient temperature of a least 30 min the signal was read on a Perkin Elmer Discovery fluorimeter.

The effect of IKK- $\beta$  inhibitors on primary synovial fibroblast mediator production was assessed as follows: Primary cultures of human RSF were obtained  
15 by enzymatic digestion of synovium obtained from adult patients with rheumatoid arthritis as previously described (Roshak *et al.*, 1996b). Cells were cultured in Earl's Minimal Essential Medium (EMEM) which contained 10% fetal bovine serum (FBS), 100 units/ml penicillin and 100  $\mu$ g/ml streptomycin (GIBCO, Grand Island, NY), at 37°C and 5% CO<sub>2</sub>. Cultures were used at passages 4 through 9 in order to  
20 obtain a more uniform type B fibroblast population. For some studies, fibroblasts were plated at  $5 \times 10^4$  cells/mL in 16 mm (diameter) 24 well plates (Costar, Cambridge, MA). Cells (70-80% confluence) were exposed to IL-1 $\beta$  (1 ng/mL) (Genzyme, Cambridge, MA) for the designated time. Drugs in DMSO vehicle (1%) were added to the cell cultures 15 minutes prior to the addition of IL-1. Studies were  
25 conducted 3-4 times using synovial cells from different donors. RSF cellular extracts were prepared from cells treated as described above. Briefly, human RSF were removed by trypsin/EDTA, washed, and harvested by centrifugation. Cellular extracts were prepared as previously described (Dignam *et al.*, 1983; Osborn, *et al.*, 1989). Briefly, at the end of the incubation period the cells ( $1 \times 10^7$  cells) were  
30 washed 2x in PBS without Ca<sup>2+</sup> and Mg<sup>2+</sup>. The resulting cell pellets were

resuspended in 20  $\mu$ L of Buffer A (10 mM Hepes (pH 7.9), 10 mM KCl, 1.5 mM  $MgCl_2$ , 0.5 mM.

Effect of IKK- $\beta$  inhibition on human monocyte stimulated eicosanoid and cytokine production was assessed as follows: Monocytes were isolated from  
5 heparinized whole blood by double gradient centrifugation as previously described. Isolated monocyte enriched PBMCs were then adhered to 24 well culture plates at  $2 \times 10^6$  cells/mL in RPMI 1640 10% FBS (Hyclone, Logan, Utah) for 2 h. to further enrich the monocyte population. The media was then removed, cells washed once with RPMI 1640, and 1 mL RPMI 1640 10% FBS was added to the wells. Test  
10 compounds are added to the wells with a final vehicle concentration of 0.05% DMSO. Monocytes were activated by the addition of 200 ng/mL endotoxin (LPS; *E. coli* serotype 026:B6)(Sigma, St. Louis, MO.) and incubated for 24 hrs. Cell-free supernates were analyzed by ELISA for TNF- $\alpha$  (EIA developed at SB), PGE<sub>2</sub> (Cayman Chemical, Ann Arbor, MI), and IL-8 and IL-6 Biosource International,  
15 Camarillo, CA). Viability of the cells was determined by trypan blue exclusion.

Effect of IKK- $\beta$  inhibitors on phorbol ester-induced inflammation was assessed as follows: The inflammatory response induced by the cutaneous application of phorbol ester (PMA) to the external pinnae of Balb/c mice has proven to be a useful model to examine multifactorial inflammatory cell infiltration and  
20 inflammatory alteration of epidermis. The intense inflammatory lesion is dominated by neutrophil infiltration, which can be easily quantified by measurement tissue concentration myeloperoxidase, an azuriphilic granular enzyme present in neutrophils. In addition, the overall intensity of the inflammatory response can be measured by determination of ear thickness. Balb/c mice ( $n = 6$ /group) were  
25 administered drug treatment or vehicle followed by PMA (4  $\mu$ g/ear). The mice were sacrificed 4 h. later, the ear thickness determined and NF- $\kappa$ B activation was monitored by I $\kappa$ B $\alpha$  western or EMSA analysis.

Effect of IKK- $\beta$  inhibitors on rat carrageenan-induced paw edema was assessed as follows: Male Lewis rats (Charles River- Raleigh, NC) were housed and  
30 allowed free access to food and water, and weighed between 200-275g for each experiment. Compound or vehicle (0.5% Tragacanth (p.o.) or 10%DMSO,

5%DMA, 30% Cremophor(i.p.)) was administered 30 minutes to 1 hour prior to the carrageenan injection. Edema was induced by injection of 1% carrageenan in sterile dH<sub>2</sub>O (0.05ml/paw) into the plantar surface of the right hindpaw. Paw thickness was measured prior to administration of compound or vehicle, and again at 3 hours, to determine change in paw volume. Rats were euthanized by CO<sub>2</sub> inhalation and the right hindfoot was removed, immediately frozen in liquid nitrogen and stored at -80C for analysis.

To determine the effects of an IKK-2 inhibitor in the mouse collagen-induced arthritis (CIA) model, 12 male DBA/1 mice (20-22 grams) per treatment group were immunized on day 0 with a total of 100 uL of complete Freund's adjuvant (CFA) containing 200 ug of bovine type II collagen. On day 21 mice were boosted with 100 uL of phosphate buffered saline (PBS) containing 200 ug of bovine type II collagen (the 100 uL of collagen/CFA or collagen/PBS was injected subcutaneously into the tail). The IKK-2 inhibitor in vehicle, or vehicle alone, was administered intraperitoneally, twice daily, from days 1 through 40 (disease symptoms are evident beginning on days 25-28). Two additional treatment groups included the positive control etanercept (Enbrel) (4 mg/kg, intraperitoneally, every other day), and the etanercept vehicle (PBS). Mice were scored daily, through day 50, for clinical symptoms (see below), and paw thicknesses were measured. In addition to the 12 mice per treatment group that were scored throughout the experiment, at several time points during the course of disease satellite mice (3-5 per treatment group) treated as described above were utilized to measure cytokine/chemokine levels and p65 levels in the paw, the *ex vivo* antigen recall response by draining lymph node cells/splenocytes, and histological changes in the joint.

25

**Induction of arthritis** AIA is induced by a single injection of 0.75 mg of *Mycobacterium butyricum* (Difco, Detroit, MI) suspended in paraffin oil into the base of the tail of male Lewis rats aged 6-8 weeks (160-180 g). Hindpaw volumes are measured by a water displacement method on day 16 and/or day 20. Test compounds were homogenized in a suitable vehicle and administered by a suitable route. Control animals are administered vehicles alone. Two dosing protocols are

30

generally used: prophylactic dosing, which is initiated on the day of adjuvant injection and therapeutic administration, initiated on day 10 once inflammation has been established.

#### Clinical scoring

- 5 Each paw was assigned a score ranging from 0-4, based on the following criteria:
- 0 = no inflammation
  - 1 = single swollen digit
  - 2 = several swollen digits, mild paw swelling
  - 3 = several swollen digits, moderate paw swelling
  - 10 4 = all digits swollen, severe paw swelling

#### Examples and Experimental

##### General

- Nuclear magnetic resonance spectra were recorded at either 250, 300 or 400
- 15 MHz using, respectively, a Bruker AM 250, Bruker ARX 300 or Bruker AC 400 spectrometer.  $\text{CDCl}_3$  is deuteriochloroform,  $\text{DMSO-d}_6$  is hexadeuteriodimethylsulfoxide, and  $\text{CD}_3\text{OD}$  is tetradeuteriomethanol. Chemical shifts are reported in parts per million ( $\delta$ ) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d =
- 20 doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and
- 25 FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers ( $\text{cm}^{-1}$ ). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-
- 30 Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

Where indicated, certain of the materials were purchased from the Aldrich  
5 Chemical Co., Milwaukee, Wisconsin, TCI America, Portland, OR..

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

10 The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the  
15 Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

#### Example 1

20 **2-Amino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide trifluoroacetate**  
Morpholine (1 mL) was added dropwise to a stirred solution of cyanoacetamide (0.84 g, 0.01 mol), sulfur (0.36, 0.012 mol), and 2-indanone (1.32 g, 0.01 mmol) in absolute ethanol (5 mL). The resulting solution was stirred at 60 °C overnight. The  
25 solvent was then removed under vacuo and the residue was taken up into ethyl acetate (10 mL), washed by water (2 x 10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under vacuo to give a dark brown solid. The product was then purified on Gilson preparative HPLC (YMC HPLC column 50 X 20 mm I.D., s-5 µm, 120 Å; gradient elution, 0.1%TFA in  
30 acetonitrile:0.1% aqueous TFA, 10:90 to 90:10, 10 min) to give the title compound as a brown solid (100 mg, 0.435 mmol, 4.3% yield). ESMS m/z: 231 [M+H]<sup>+</sup>.



### Example 2

#### **2-Ureido-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide**

Chlorosulfonyl isocyanate (0.025 g, 0.17 mL) was added dropwise to a stirred  
5 solution of 2-amino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide  
trifluoroacetate (0.040 g, 0.17 mmol) in dry dichloromethane (2 mL). The resulting  
reaction mixture was stirred under nitrogen for 30 min. Water (0.5 mL) was then  
added to the reaction mixture and the reaction mixture was allowed to stir an  
additional 10 minutes before the solvent was removed under vacuo. The residue was  
10 then purified on Gilson preparative HPLC (YMC HPLC column 50 X 20 mm I.D., s-  
5  $\mu$ m, 120 Å; gradient elution, 0.1%TFA in acetonitrile: 0.1% aqueous TFA, 10:90  
to 90:10, 10 min) to give title compound as brown solid (0.020 g, 0.435 mmol,  
43.5% yield). ESMS  $m/z$ : 274 [M+H]<sup>+</sup>.

15

### Example 3

#### **2-Acetylamino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide**

Acetyl chloride (0.039 g, 0.5 mmol) was added dropwise to a stirred solution of 2-  
amino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide(0.115 g, 0.5 mmol) in  
20 dry pyridine (3 mL) at room temperature. The resulting reaction mixture was stirred  
under nitrogen for 2 h. Ethyl ether (20 mL) was then added to the reaction mixture.  
The reaction mixture was allowed to stir an additional 10 minutes. The reaction  
mixture was then filtered, washed with excess ethyl ether, air dried to give the title  
compound as light brown solid (0.082 g, 0.435 mmol, 60.3% yield). ESMS  $m/z$ :  
25 273 [M+H]<sup>+</sup>.

### Example 4

#### **2-Amino-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide**

The title compound was prepared by the same procedure as Example 1 except that 2-  
30 indanone was replaced with beta-tetralone to give the above title compound as  
brown solid. ESMS  $m/z$ : 245 [M+H]<sup>+</sup>.

**Example 5****2-Acetylamino-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide**

- 5 The title compound was prepared by the same procedure as Example 3 except that 2-amino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide was replaced with 2-amino-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide to give the above title compound as brown solid. ESMS  $m/z$ : 287  $[M+H]^+$ .

**Example 6****2-Ureido-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide**

- 10 The title compound was prepared by the same procedure as Example 2 except that 2-amino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide was replaced with 2-amino-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide to give the above title compound as brown solid. ESMS  $m/z$ : 288  $[M+H]^+$ .

**Example 7****2-Amino-8-methoxy-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide trifluoroacetate**

- 20 The title compound was prepared by the same procedure as Example 1 except that 2-indanone was replaced with 7-methoxy-2-tetralone to give the above title compound as light grey solid ESMS  $m/z$ : 275  $[M+H]^+$ .

**Example 8****8-Methoxy-2-ureido-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide**

- 30 The title compound was prepared by the same procedure as Example 2 except that 2-amino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide was replaced with 2-amino-8-methoxy-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide trifluoroacetate to give the above title compound as brown solid. ESMS  $m/z$ : 318  $[M+H]^+$ .

35

**Example 9****2-Amino-7-methoxy-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide**

5 Morpholine (0.57 mL) was added dropwise to a stirred solution of cyanoacetamide (0.48 g, 5.7 mmol), sulfur (0.20, 6.24 mmol), and 6-methoxy-2-tetralone (1.00 g, 5.7 mmol) in absolute ethanol (3 mL). The resulting solution was stirred at 70 °C overnight. The solvent was then removed under vacuo and the residue was taken up into ethyl acetate (10 mL), washed by water (2 x 10 mL) and brine (10 mL), dried  
10 over anhydrous magnesium sulfate, filtered and concentrated under vacuo to give a dark brown oil. The residual oil was purified by flash chromatography (silic gel, 75% ethyl acetate/hexane ) to give the title compound as light grey solid (0.12 g, 0.437 mmol, 7.6% yield). ESMS  $m/z$ : 275  $[M+H]^+$ .

**Example 10****2-Acetylamino-7-methoxy-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide**

The title compound was prepared by the same procedure as Example 3 except that 2-amino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide was replaced with 2-  
20 amino-7-methoxy-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide to give the above title compound as light grey solid. ESMS  $m/z$ : 317  $[M+H]^+$ .

**Example 11****2-Amino-7-bromo-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide**

The title compound was prepared by the same procedure as Example 9 except 6-methoxy-2-tetralone was replaced with 6-bromo-2-tetralone to give the above title compound as light grey solid. ESMS  $m/z$ : 324  $[M+H]^+$ .

**Example 12****2-Acetylamino-7-bromo-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide**

The title compound was prepared by the same procedure as Example 3 except  
35 that 2-

amino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide was replaced with 2-amino-7-bromo-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide to give the above title compound as light grey solid. ESMS  $m/z$ : 366  $[M+H]^+$ .

5

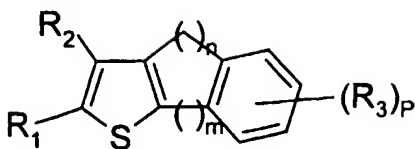
**Example 13**

**7-Bromo-2-ureido-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide** The title compound was prepared by the same procedure as Example 2 except 2-amino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide was replaced with 2-amino-7-bromo-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide trifluoroacetate to give the above title compound as brown solid. ESMS  $m/z$ : 367  $[M+H]^+$ .

10

What is claimed is:

1. A compound of formula (I):



( I )

5 wherein:

$R_1$  represents  $NR_4R_5$ ;

$R_2$  represents  $CONH_2$  or  $SO_2NH_2$ ;

$R_3$  is selected from the group consisting of halogen,  $C_{1-4}$ alkyl,  $NH_2$ ,  $CF_3$ ,  $OCF_3$ ,  
O-alkyl, S-alkyl, CN, CHO,  $SO_2$ -alkyl,  $(CH_2)_qNR_7R_8$ , O- $(CH_2)_qNR_7R_8$ ,  $(CH_2)_q$ -  
10 aryl, O- $(CH_2)_q$ -aryl,  $(CH_2)_q$ -heteroaryl, O- $(CH_2)_q$ -heteroaryl,  $(CH_2)_q$ -heteroalkyl,  
O- $(CH_2)_q$ -heteroalkyl and  $NO_2$ ;

$R_4$  represents H or  $C_{1-4}$ alkyl;

$R_5$  represents H or  $CONHR_6$ ;

$R_6$  is selected from the group consisting of hydrogen, alkyl and aryl;

15  $R_7$  represents  $C_{1-4}$ alkyl;

$R_8$  represents  $C_{1-4}$ alkyl;

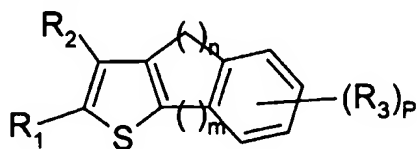
m is 0, 1, 2 or 3;

n is 0, 1, 2, or 3;

p is 1, 2 or 3; and

20 q is 1, 2, 3 or 4; or a pharmaceutically acceptable salt thereof.

2. A compound of formula (Ia):



( Ia )

wherein:

R<sub>1</sub> represents NR<sub>4</sub>R<sub>5</sub>;

R<sub>2</sub> represents CONH<sub>2</sub>;

R<sub>3</sub> is selected from the group consisting of halogen, C<sub>1-4</sub>alkyl, NH<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>,

5 O-alkyl, S-alkyl, CN, CHO, SO<sub>2</sub>-alkyl, (CH<sub>2</sub>)<sub>q</sub>NR<sub>7</sub>R<sub>8</sub>, O-(CH<sub>2</sub>)<sub>q</sub>NR<sub>7</sub>R<sub>8</sub>, (CH<sub>2</sub>)<sub>q</sub>-aryl, O-(CH<sub>2</sub>)<sub>q</sub>-aryl, (CH<sub>2</sub>)<sub>q</sub>-heteroaryl, O-(CH<sub>2</sub>)<sub>q</sub>-heteroaryl, (CH<sub>2</sub>)<sub>q</sub>-heteroalkyl, O-(CH<sub>2</sub>)<sub>q</sub>-heteroalkyl and NO<sub>2</sub>;

R<sub>4</sub> represents H;

R<sub>5</sub> represents CONHR<sub>6</sub>;

10 R<sub>6</sub> represents H;

R<sub>7</sub> represents C<sub>1-4</sub>alkyl;

R<sub>8</sub> represents C<sub>1-4</sub>alkyl;

m is 0;

n is 1 or 2;

15 p is 1, or 2; and

q is 1, 2, 3 or 4; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 wherein the compound is selected from the group consisting of:

20 2-Amino-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide;

2-Ureido-4H-indeno[1,2-*b*]thiophene-3-carboxylic acid amide;

2-Acetylamino-4H-indeno[1,2*b*]thiophene-3-carboxylic acid amide;

2-Amino-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;

2-Acetylamino-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;

25 2-Ureido-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;

2-Amino-8-methoxy-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;

8-Methoxy-2-ureido-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;

2-Amino-7-methoxy-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;

2-Acetylamino-7-methoxy-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid

30 amide;

2-Amino-7-bromo-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide;

2-Acetylamino-7-bromo-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide; and

7-Bromo-2-ureido-4,5-dihydro-naphtho[1,2-*b*]thiophene-3-carboxylic acid amide; or a pharmaceutially acceptable salt thereof.

5

4. A method of treating a disease characterized by pathological NF- $\kappa$ B activation comprising inhibiting the pathological activation by administering to a patient in need thereof an effective amount of a compound according to claim 1.

10 5. A method according to claim 3 wherein the disease is an inflammatory or tissue repair disorder.

6. A method according to Claim 4 wherein the disease is selected from the group consisting of inflammatory and tissue repair disorders, particularly rheumatoid  
15 arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease) osteoarthritis, osteoporosis and fibrotic diseases, dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage, autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection,  
20 Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease, cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome, and Ataxia Telangiectasia.

7. A method according to Claim 3 wherein said disease is dermatosis.

25

8. A method according to Claim 3 wherein the disease is selected from the group consisting of: psoriasis, atopic dermatitis, and UV-induced skin damage.

9. A method according to Claim 3 wherein the disease is selected from the  
30 group consisting of autoimmune diseases; tissue and organ rejection, Alzheimer's

disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, osteoarthritis, osteoporosis, and Ataxia Telangiectasia.

10. A method according to Claim 3 wherein said disease is an autoimmune  
5 disease.

11. A method according to Claim 3 wherein the autoimmune disease is systemic  
lupus erythematosus, multiple sclerosis, psoriatic arthritis, or ankylosing spondylitis,  
diabetes

10

12. A method according to any one of Claim 1 wherein the disease is cancer and  
or cachexia.

13. A method according to Claim 3 wherein the cancer is Hodgkins disease.  
15

14. A method according to Claim 3 wherein the disease is inflammation  
associated with infection and certain viral infections, including acquired immune  
deficiency syndrome (AIDS).

20 15. A method according to Claim 3 wherein the disease is AIDS.

16. A method according to Claim 3 wherein the disease is adult respiratory  
distress syndrome.

17. A method according to Claim 3 wherein there is dual inhibition of NF- $\kappa$ B  
25 and checkpoint kinase.



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(72) Inventors; and

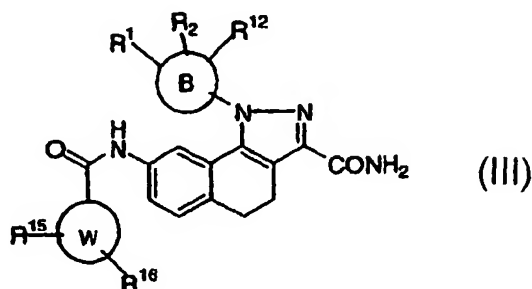
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(54) Title: SUBSTITUTED PYRAZOLYL COMPOUNDS FOR THE TREATMENT OF INFLAMMATION



(57) Abstract: The present invention relates to substituted pyrazolyl derivatives of Formula III, compositions comprising such, intermediates, methods of making substituted pyrazolyl derivatives, and methods for treating cancer, inflammation, and inflammation-associated disorders, such as arthritis.

## SUBSTITUTED PYRAZOLYL COMPOUNDS FOR THE TREATMENT OF INFLAMMATION

5 The present application claims priority under Title 35, United States Code, §119 to  
United States Provisional application Serial No. 60/379,090, filed May 9, 2002, and  
PCT/US 02/29774, filed September 19, 2002, both of which are incorporated by  
reference in their entirety as if written herein.

### FIELD OF THE INVENTION

10

[001] The present invention in general is in the field of anti-inflammatory  
pharmaceutical agents and specifically relates to substituted pyrazolyl derivatives,  
compositions comprising such, and methods for treating cancer, inflammation, and  
inflammation-associated disorders, such as arthritis.

15

### BACKGROUND OF THE INVENTION

[002] The following description of the background of the invention is provided  
to aid in the understanding the invention, but is not admitted to be or describe prior  
20 art to the invention.

[003] NF- $\kappa$ B is a ubiquitous transcription factor that plays a prominent role in  
the activation of the immune system and in stress responses by regulating the  
transcription of many early, inducible genes including proinflammatory cytokines,  
25 adhesion molecules, growth factors, enzymes, and receptors (Ghosh S., May, M. J.,  
and Kopp, E (1998) *Annu. Rev. Immunol.* 16, 115-260; Zandi, E., and Karin, M.  
(1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-  
27342). Specificity of gene expression is determined at a cellular level by a diverse  
array of external stimuli such as bacterial products including LPS, as well as  
30 cytokines, most importantly tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) and interleukin- $\beta$   
(IL1 $\beta$ ). Through the synergistic interaction with other transcription factors, further  
specificity can be achieved while maintaining enormous potential to coordinately

induce a large number of functionally related genes. NF- $\kappa$ B is composed of homo and heterodimers of the Rel protein family and is sequestered in an inactive form in the cytoplasm by members of the I $\kappa$ B family of inhibitory proteins (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* 16, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-27342). I $\kappa$ Bs mask the nuclear localization signal on NF- $\kappa$ B, preventing nuclear translocation and hence DNA binding to the promoter regions of responsive genes. Stimulation of cells with an agonist that activates NF- $\kappa$ B leads to a series of biochemical signals, ultimately resulting in the phosphorylation, ubiquitinylation, and degradation of I $\kappa$ Bs, thereby releasing NF- $\kappa$ B for nuclear translocation (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* 16, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-27342). Recently, two I $\kappa$ B kinases (IKK1 or IKK $\alpha$  and IKK2 or IKK $\beta$ ), which phosphorylate I $\kappa$ Bs and thereby initiate their degradation, have been cloned and characterized by a number of laboratories (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* 16, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-27342). The catalytic subunits, IKK1 and IKK2, are similar structurally as well as enzymatically and exist as a heterodimer in a large protein complex referred to as the IKK signalsome (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* 90, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* 388, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* 278, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. And Goeddel, D.V. (1997) *Science* 278, 866-869). A third protein, NEMO (IKK $\gamma$ , IKKAP1), is a regulatory adapter protein necessary for IKK activation and kinase activity (Yamaoka, S., Courtois, G., Bessia, C., Whiteside, S. T., Weil, R., Agou, F., Kirk, H. E., Kay, R. J., and Ireal, A. (1998) *Cell* 93, 1231-1240; Rothwarf, D. M., Zandi, E., Natoli, G., Karin, M. (1998) *Nature* 395, 297; Mercurio, F., Murray, B. W., Shevchenko, A., Bennet, B. L., Young, D. B., Li, J. W., Pascual, G., Motiwala, A., Zhu, H., Mann,

M and Manning, A. M. (1999) *Mol. Cell. Biol.* 2, 1526-1538). IKK1 and IKK2 are co-expressed in most human adult tissues as well as in different developmental stages of mouse embryos (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* 90, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* 388, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* 278, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* 278, 866-869; Hu, M. C. T., and Wang, Y. (1998) *Gene* 222, 31-40). This kinase complex appears to represent a critical, common denominator in the activation of NF- $\kappa$ B in a number of signal transduction pathways stimulated by a variety of agonists including cytokines, such as TNF $\alpha$  and IL1 $\beta$ , microbial products such as LPS and viral proteins such as TAX, as well as phorbol esters, oxidizing agents and serine/tyrosine phosphatases (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* 16, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-27342).

[004] IKK1 (also termed IKK $\alpha$ , Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* 90, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* 388, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. And Roa, A. (1997) *Science* 278, 860-866) was cloned simultaneously by standard biochemical purification of the I $\kappa$ B kinase activity from TNF $\alpha$  stimulated HeLa S3 cells and by its interaction with the MAP3K, NF- $\kappa$ B inducing kinase (NIK), in a yeast two-hybrid screen. IKK1 was identified as the previously cloned serine-threonine kinase, CHUK (Connelly, M. and Marcu, K. (1995) *Cell. Mol. Biol. Res.* 41, 537-549). IKK1 (also termed IKK $\alpha$ ) is an 85 kDa, 745 amino acid protein that contains an N-terminal serine/threonine kinase catalytic domain, a leucine zipper-like amphipathic helix, and a C-terminal helix-loop-helix domain. IKK2 (also termed IKK $\beta$ ) was also cloned by standard biochemical purification, copurifying with IKK1 from TNF $\alpha$

stimulated HeLa S3 cells as well as by being identified in the public database from an EST clone with sequence homology to IKK1 (Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* 278, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. And Goeddel, D.V. (1997) *Science* 278, 866-869). IKK2 is an 87 kDa, 756 amino acid protein with the same over all topology as IKK1 except for the addition of an 11 amino acid extension at the C-terminus. IKK1 and IKK2 are 52% identical overall with 65% identity in the kinase domain and 44% identity in the protein interaction domains in the C-terminus. Data obtained using transient mammalian expression analysis, by *in vitro* translation experiments and by coexpression in a baculoviral system reveals that IKK1 and IKK2 associate preferentially as a heterodimer through their leucine zipper motifs. Although homodimers have also been described in these systems, the heterodimer is thought to be the physiologic form of the kinase in mammalian cells (Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Li, J., Peet, G.W., Pullen, S.S., Schembri-King, J., Warren, T.C., Marcu, K.B., Kehry, M.R., Barton, R. and Jakes, S. (1998) *J. Biol. Chem.* 273, 30736-30741). Finally, NEMO (also termed IKK $\gamma$ ) contains three  $\alpha$ -helical regions including a leucine zipper, interacts preferentially with IKK2 and is required for activation of the heterodimeric kinase complex perhaps by bringing other proteins into the signalsome complex (Yamaoka, S., Courtois, G., Bessia, C., Whiteside, S. T., Weil, R., Agou, F., Kirk, H. E., Kay, R. J., and Ireal, A. (1998) *Cell* 93, 1231-1240; Rothwarf, D. M., Zandi, E., Natoli, G., Karin, M. (1998) *Nature* 395, 297; Mercurio, F., Murray, B. W., Shevchenko, A., Bennet, B. L., Young, D. B., Li, J. W., Pascual, G., Motiwala, A., Zhu, H., Mann, M and Manning, A. M. (1999) *Mol. Cell. Biol.* 2, 1526-1538).

[005] The kinase activities of IKK1 and IKK2 are regulated by phosphorylation and require an intact leucine zipper (LZ) for dimerization as well as an intact helix-loop-helix (HLH) domain, which can exert a positive regulatory effect on kinase activity even when it is expressed in trans with the remainder of the

- IKK protein (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* 90, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* 388, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M.,
- 5 Manning, A. and Roa, A. (1997) *Science* 278, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* 278, 866-869; Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* 284, 309-313).
- Both IKK subunits contain a canonical MAPKK activation loop motif near the N-
- 10 terminus which is the target for phosphorylation and activation of kinase activity by MAP3Ks such as NIK and MEKK1, although the physiologic regulation by these two upstream kinases awaits further characterization (Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* 19, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* 274, 27339-27342; Karin, M., and Delhase, M. (1998) *Proc. Natl. Acad. Sci. USA* 95, 9067-
- 15 9069). Finally, phosphorylation of serines in the C-terminus of IKK2 results in a decrease in IKK activity and it is postulated to be responsible for the transient kinase activity seen after stimulation of cells with an agonist (Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* 284, 309-313).
- 20 [006] IKK2 demonstrates a more potent kinase activity compared to IKK1 using I $\kappa$ B $\alpha$  or I $\kappa$ B $\beta$  as a substrate (Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* 278, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* 91, 243-252; Woronicz, J.D.,
- 25 Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* 278, 866-869; Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* 284, 309-313).
- Mutations of the phospho-acceptor serine residues within the MAPKK activation loop alters IKK2 kinase activity; the serine to alanine substitutions result in decreased kinase activity whereas the serine to glutamic acid substitutions result in
- 30 a constitutively active kinase. Similar alanine mutations in IKK1 do not result in a decreased stimulation of total IKK activity in response to TNF $\alpha$  or IL1 $\beta$  (Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* 284, 309-313). IKK2



being the dominant kinase activity within the IKK complex is further supported by the analysis of fibroblasts from mice deficient in IKK1 or IKK2. Fibroblasts lacking IKK1 retain full IKK activity in response to cytokines and could activate NF- $\kappa$ B. In contrast, fibroblasts lacking IKK2 do not exhibit IKK activity when

5 stimulated with cytokines nor do they activate NF- $\kappa$ B. Furthermore, the phenotypes of each IKK knock out is unique with IKK1 deficiency resulting in skin and skeletal defects and IKK2 knock out being embryonic lethal due to hepatocyte apoptosis (Li, Q., Antwerp, D. V., Mercurio, F., Lee, K., and Verma, I. M. (1999) *Science* 284, 321-325; Takeda, K., Tekeuchi, O., Tsujimura, T., Itami, S., Adachi, O., Kawai, T.,

10 Sanjo, H., Yoshikawa, K., Terada, N., and Akira, S. (1999) *Science* 284, 313-316; Hu, Y., Baud, V., Delhase, M., Zhang, P., Deerinck, T., Ellisman, M., Johnson, R., and Karin, M. (1999) *Science* 284, 315-320; Li, Q., Lu, Q., Hwang, J. Y., Buscher, D., Lee, K., Izpisua-Belmonte, J. C., and Verma, I. M. (1999) *Gene and Development* 13, 1322-1328; Tanaka, M., Fuentes, M. E., Yamaguchi, K., Durnin, M. H., Dalrymple, S. A., Hardy, K. L., and Goeddel, D. V. (1999) *Immunity* 10,

15 421-429).

[007] It is well-known that NF- $\kappa$ B plays a key role in the regulated expression of a large number of pro-inflammatory mediators including cytokines such as IL-6

20 and IL-8, cell adhesion molecules, such as ICAM and VCAM, and inducible nitric oxide synthase (iNOS). Such mediators are known to play a role in the recruitment of leukocytes at sites of inflammation and in the case of iNOS, may lead to organ destruction in some inflammatory and autoimmune diseases. The importance of NF- $\kappa$ B in inflammatory disorders is further strengthened by studies of airway

25 inflammation including asthma in which NF- $\kappa$ B has been shown to be activated. This activation may underlie the increased cytokine production and leukocyte infiltration characteristic of these disorders. In addition, inhaled steroids are known to reduce airway hyperresponsiveness and suppress the inflammatory response in asthmatic airways. In light of the recent findings with regard to glucocorticoid

30 inhibition of NF- $\kappa$ B, one may speculate that these effects are mediated through an inhibition of NF- $\kappa$ B. Further evidence for a role of NF- $\kappa$ B in inflammatory disorders comes from studies of rheumatoid synovium. Although NF- $\kappa$ B is

normally present as an inactive cytoplasmic complex, recent immunohistochemical studies have indicated that NF- $\kappa$ B is present in the nuclei, and hence active, in the cells comprising rheumatoid synovium. Furthermore, NF- $\kappa$ B has been shown to be activated in human synovial cells in response to stimulation with TNF- $\alpha$ . Such a  
5 distribution may be the underlying mechanism for the increased cytokine and eicosanoid production characteristic of this tissue. See Roshak, A. K., et al., *J. Biol. Chem.*, 271, 31496-31501 (1996).

[008] The NF- $\kappa$ B/Rel and I $\kappa$ B proteins are also likely to play a key role in  
10 neoplastic transformation. Family members are associated with cell transformation in vitro and in vivo because of overexpression, gene amplification, gene rearrangements, or translocations (Gillmore TD, *Trends Genet* 7:318-322, 1991; Gillmore TD, *Oncogene* 18:6925-6937, 1999; Rayet B. et al., *Oncogene* 18: 6938-6947, 1991). In addition, rearrangement and/or amplification of the genes encoding  
15 these proteins are seen in 20-25% of certain human lymphoid tumors. In addition, a role for NF- $\kappa$ B in the regulation of apoptosis, cell cycle progression, invasion, and metastasis has been reported (Bours V. et al., *Biochemical Pharmacology* 60:1085-1090, 2000) strengthening the role of this transcription factor in the control of cell proliferation. The inhibition of NF- $\kappa$ B has been shown to potentiate TNF- and  
20 cancer therapy through increased apoptosis (Wang C-Y et al., *Science* 274:784-787, 1996; Wang C-Y et al., *Nat Med* 5:412-417, 1999). It has also been shown that human T-cell leukemia virus type 1 (HTLV1) infected cells (the etiological agent of an aggressive malignancy of activated CD4<sup>+</sup> T lymphocytes), IKK $\alpha$  and IKK $\beta$  are expressed constitutively, which normally function in a transient manner (Chu Z-L et al., *J of Biological Chemistry* 273:15891-15894, 1998). The HTLV1 transforming  
25 and transactivating protein (Tax) has been shown to bind MEKK1 and increases the activity of IKK $\beta$  to enhance phosphorylation of serine residues in I $\kappa$ B $\alpha$  that lead to its degradation.

30 [009] Pyrazoles have been described for use in the treatment of inflammation. U.S. Patent No. 5,134,142 to Matsuo et al describes 1,5-diaryl pyrazoles, and

specifically, 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-trifluoromethyl pyrazole, as having anti-inflammatory activity.

[0010] U.S. Patent No. 3,940,418 to R. Hamilton describes tricyclic 4,5-dihydrobenz[g]indazoles as antiinflammatory agents. In addition, R. Hamilton [*J. Heterocyclic Chem.*, 13, 545 (1976)] describes tricyclic 4,5-dihydrobenz[g]indazoles as antiinflammatory agents. U.S. Patent No. 5,134,155 describes fused tricyclic pyrazoles having a saturated ring bridging the pyrazole and a phenyl radical as HMG-CoA reductase inhibitors. European publication EP 477,049, published Mar. 25, 1992, describes [4,5-dihydro-1-phenyl-1H-benz[g]indazol-3-yl]amides as having antipsychotic activity. European publication EP 347,773, published Dec. 27, 1989, describes [4,5-dihydro-1-phenyl-1H-benz[g]indazol-3-yl]propanamides as immunostimulants. M. Hashem et al [*J. Med. Chem.*, 19, 229 (1976)] describes fused tricyclic pyrazoles, having a saturated ring bridging the pyrazole and a phenyl radical, as antibiotics.

[0011] Certain substituted pyrazolyl-benzenesulfonamides have been described in the literature as synthetic intermediates. Specifically, 4-[5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound as an intermediate for compounds having hypoglycemic activity [R. Soliman et al, *J. Pharm. Sci.*, 76, 626 (1987)]. 4-[5-[2-(4-Bromophenyl)-2H-1,2,3-triazol-4-yl]-3-methyl-1H-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound and described as potentially having hypoglycemic activity [H. Mokhtar, *Pak. J. Sci. Ind. Res.*, 31, 762 (1988)]. Similarly, 4-[4-bromo-5-[2-(4-chlorophenyl)-2H-1,2,3-triazol-4-yl]-3-methyl-1H-pyrazol-1-yl]benzenesulfonamide has been prepared [H. Mokhtar et al, *Pak. J. Sci. Ind. Res.*, 34, 9 (1991)].

[0012] The phytotoxicity of pyrazole derivatives is described [M. Cocco et al, *Il. Farmaco-Ed. Sci.*, 40, 272 (1985)], specifically for 1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazole-3,4-dicarboxylic acid.

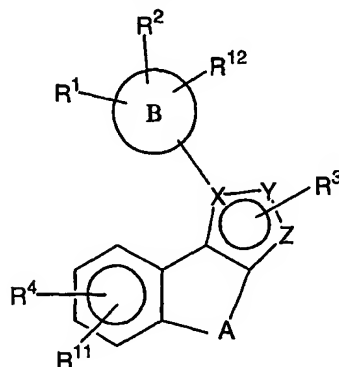
[0013] The use of styryl pyrazole esters for antidiabetes drugs is described [H. Mokhtar et al, *Pharmazie*, 33, 649-651 (1978)]. The use of styryl pyrazole carboxylic acids for antidiabetes drugs is described [R. Soliman et al, *Pharmazie*, 33, 184-5 (1978)]. The use of 4-[3,4,5-trisubstituted-pyrazol-1-yl]benzenesulfonamides as intermediates for sulfonylurea anti-diabetes agents is described, and specifically, 1-[4-(aminosulfonyl)phenyl]-3-methyl-5-phenyl-1*H*-pyrazole-4-carboxylic acid [R. Soliman et al, *J. Pharm. Sci.*, 72, 1004 (1983)]. A series of 4-[3-substituted methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamides has been prepared as intermediates for anti-diabetes agents, and more specifically, 4-[3-methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide [H. Feid-Allah, *Pharmazie*, 36, 754 (1981)]. In addition, 1-(4-[aminosulfonyl]phenyl)-5-phenylpyrazole-3-carboxylic acid has been prepared from the above described 4-[3-methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide compound [R. Soliman et al, *J. Pharm. Sci.*, 70, 602 (1981)].

[0014] WO 00/27822 discloses tricyclic pyrazole derivatives, WO 00/59901 discloses dihydroindeno pyrazoles, WO 99/17769 discloses indeno[1,2-*c*]-, naphtho[1,2-*c*]- and benzo[6,7]cyclohepta[1,2-*c*]pyrazole derivatives, US 5,196,445 discloses heteroaryl-3-oxo-propanenitrile derivatives useful in the treatment of rheumatoid arthritis, WO 97/10210 discloses tricyclic pyrrolidine derivatives as calcium channel antagonists, WO 95/15315 discloses diphenyl pyrazole compounds, WO 95/15317 discloses triphenyl pyrazole compounds, WO 95/15318 discloses tri-substituted pyrazole compounds, and WO 96/09293 discloses benz[*g*]indazolyl derivatives.

[0015] WO 95/15316 discloses substituted pyrazolyl benzenesulfonamide derivatives and WO 01/32663 discloses pyrazolecarboxylic acid tricyclic derivatives as CB<sub>1</sub> cannabinoid receptor inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

**[0016]** A class of compounds, which are useful in treating cancer, inflammation, and inflammation related disorders, is defined by Formula I:



5

wherein

**A** is  $(\text{CH}_2)_m$ ; wherein each  $\text{CH}_2$  may be independently substituted with one or more substitution selected from the group consisting of: aryl, heteroaryl, alkanoyl, hydroxy, halogen, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

10

**m** is 1 to 4;

15

**B** is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic wherein said aryl, heteroaryl, or heterocyclic are optionally substituted with  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^{12}$ ;

**X** is selected from the group consisting of: N and C;

**Y** and **Z** are independently selected from the group consisting of: N, CH,  $\text{CR}^3$ , S, and O;

20

**R**<sup>1</sup> is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN,  $\text{NO}_2$ ,  $\text{OR}^5$ ,  $\text{OCOOR}^5$ ,  $\text{CO}_2\text{R}^7$ ,  $\text{CON}(\text{R}^6)\text{R}^7$ ,  $\text{COR}^6$ ,  $\text{SR}^6$ ,  $\text{SOR}^6$ ,  $\text{SO}_2\text{R}^6$ ,  $\text{NR}^6\text{R}^7$ ,  $\text{NR}^6\text{COR}^7$ ,  $\text{NR}^6\text{CONHR}^7$ ,  $\text{NR}^6\text{SO}_2\text{R}^7$ ,  $\text{NR}^6\text{SO}_2\text{NHR}^7$ , and  $\text{SO}_2\text{N}(\text{R}^6)\text{R}^7$  wherein  $\text{R}^6$  and  $\text{R}^7$  may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO,  $\text{SO}_2$ , O,

25

- and  $\text{NR}^6$ ; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or  $\text{OR}^5$  are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl,  $\text{COCF}_3$ ,  $\text{CN}$ ,  $\text{NO}_2$ ,  $\text{OR}^5$ ,  $\text{OCOOR}^5$ ,  $\text{CO}_2\text{R}^7$ ,  $\text{CON}(\text{R}^6)\text{R}^7$ ,  $\text{COR}^6$ ,  $\text{SR}^6$ ,  $\text{SOR}^6$ ,  $\text{SO}_2\text{R}^6$ ,  $\text{NR}^6\text{R}^7$ ,  $\text{NR}^6\text{COR}^7$ ,  $\text{NR}^6\text{CONHR}^7$ ,  $\text{NR}^6\text{SO}_2\text{R}^7$ ,  $\text{NR}^6\text{SO}_2\text{NHR}^7$ , and  $\text{SO}_2\text{N}(\text{R}^6)\text{R}^7$  wherein  $\text{R}^6$  and  $\text{R}^7$  may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO,  $\text{SO}_2$ , O, and  $\text{NR}^6$ ;
- $\text{R}^2$  is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl,  $\text{OR}^6$ ,  $\text{CN}$ ,  $\text{NO}_2$ ,  $\text{SR}^6$ ,  $\text{NHR}^6$ ,  $\text{CON}(\text{R}^6)\text{R}^7$ ,  $\text{NHCONHR}^6$ ,  $\text{CO}_2\text{H}$ , and haloalkyl;  
 $\text{R}^1$  and  $\text{R}^2$  may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of N, O, or S, and wherein said ring is optionally substituted with  $\text{R}^1$ ;
- $\text{R}^3$  is selected from the group consisting of: substituted or unsubstituted amidine, alkylamino, aminoalkyl,  $\text{CONHR}^7$ ,  $\text{NH}_2$ ,  $\text{NHCOR}^6$ , and  $\text{CH}_2\text{NHCOR}^6$ ;
- $\text{R}^4$  is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl,  $\text{OR}^{13}$ ,  $\text{SR}^8$ ,  $\text{SO}_2\text{N}(\text{R}^8)\text{R}^8$ ,  $\text{NHR}^9$ ,  $\text{NHCOR}^9$ ,  $\text{NR}^9\text{COR}^9$ ,  $\text{NHCO}(\text{OR}^9)$ ,  $\text{NR}^9\text{CO}(\text{OR}^9)$ ,  $\text{NR}^8\text{SO}_2\text{R}^{10}$ ,  $\text{NH}\text{SO}_2\text{N}(\text{R}^{10})\text{R}^{10'}$ ,  $\text{NR}^6\text{CON}(\text{R}^{10})\text{R}^{10'}$ ,  $\text{COR}^9$ ,  $\text{CO}_2\text{R}^8$ ,  $\text{CON}(\text{R}^8)\text{R}^8$ , wherein  $\text{R}^8$  and  $\text{R}^8$  may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO,  $\text{SO}_2$ , O, N, and  $\text{NR}^6$ , and wherein  $\text{R}^{10}$  and  $\text{R}^{10'}$  may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO,  $\text{SO}_2$ , O, N, and  $\text{NR}^6$  wherein said

aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with  $R^9$ ;

5  $R^5$  is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of  $OR^{14}$ ,  $N(R^{14})R^{14'}$ , and glycols;

10  $R^6$  is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

15  $R^7$  is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

$R^8$  is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

20  $R^{8'}$  is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

25  $R^9$  is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of:

30 alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl,

- carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkylidioxo, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;
- R<sup>10</sup>** is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,
- R<sup>10'</sup>** is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,
- R<sup>11</sup>** is selected from the group consisting of: hydrido, halogen, haloalkyl, CN, CO<sub>2</sub>R<sup>5</sup>, lower alkyl, lower alkenyl, lower alkynyl, alkoxy, and CONH<sub>2</sub>;
- R<sup>12</sup>** is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;
- R<sup>13</sup>** is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of OR<sup>14</sup>, N(R<sup>14</sup>)R<sup>14'</sup>, and glycols;



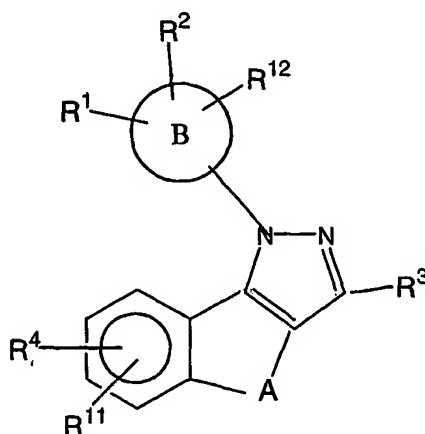
$R^{14}$  is independently selected from the group consisting of hydrido, and lower alkyl; and

$R^{14'}$  is independently selected from the group consisting of hydrido, and lower alkyl;

5

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

10 [0017] Another class of compounds is defined by Formula II



wherein

15  $A$  is  $(CH_2)_m$ ; wherein each  $CH_2$  may be independently substituted with one or more substitution selected from the group consisting of: aryl, heteroaryl, alkanoyl, hydroxy, halogen, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

$m$  is 1 to 4;

20  $B$  is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic wherein said aryl, heteroaryl, or heterocyclic are optionally substituted with  $R^1$ ,  $R^2$ , and  $R^{12}$ ;

$R^1$  is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl,  $CN$ ,  $NO_2$ ,  $OR^5$ ,

- OCOOR<sup>5</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>6</sup>)R<sup>7</sup>, COR<sup>6</sup>, SR<sup>6</sup>, SOR<sup>6</sup>, SO<sub>2</sub>R<sup>6</sup>, NR<sup>6</sup>R<sup>7</sup>,  
 NR<sup>6</sup>COR<sup>7</sup>, NR<sup>6</sup>CONHR<sup>7</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>6</sup>SO<sub>2</sub>NHR<sup>7</sup>, and  
 SO<sub>2</sub>N(R<sup>6</sup>)R<sup>7</sup> wherein R<sup>6</sup> and R<sup>7</sup> may be taken together to form a 3-7  
 membered carbocyclic ring having 1 to 3 substituted or unsubstituted  
 5 heteroatoms selected from the group consisting of: S, SO, SO<sub>2</sub>, O,  
 and NR<sup>6</sup>; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR<sup>5</sup>  
 are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl,  
 aryl, heteroaryl, haloalkyl, COCF<sub>3</sub>, CN, NO<sub>2</sub>, OR<sup>5</sup>, OCOOR<sup>5</sup>,  
 CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>6</sup>)R<sup>7</sup>, COR<sup>6</sup>, SR<sup>6</sup>, SOR<sup>6</sup>, SO<sub>2</sub>R<sup>6</sup>, NR<sup>6</sup>R<sup>7</sup>, NR<sup>6</sup>COR<sup>7</sup>,  
 10 NR<sup>6</sup>CONHR<sup>7</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>6</sup>SO<sub>2</sub>NHR<sup>7</sup>, and SO<sub>2</sub>N(R<sup>6</sup>)R<sup>7</sup> wherein  
 R<sup>6</sup> and R<sup>7</sup> may be taken together to form a 3-7 membered  
 carbocyclic ring having 1 to 3 substituted or unsubstituted  
 heteroatoms selected from the group consisting of: S, SO, SO<sub>2</sub>, O,  
 and NR<sup>6</sup>;
- 15 **R<sup>2</sup>** is selected from the group consisting of: halogen, hydrido,  
 hydroxyalkyl, alkyl, OR<sup>6</sup>, CN, NO<sub>2</sub>, SR<sup>6</sup>, NHR<sup>6</sup>, CON(R<sup>6</sup>)R<sup>7</sup>,  
 NHCONHR<sup>6</sup>, CO<sub>2</sub>H, and haloalkyl;  
 R<sup>1</sup> and R<sup>2</sup> may be taken together to form a 5 to 7 membered  
 saturated or unsaturated carbocyclic ring optionally containing 0 to 3  
 20 heteroatoms selected from the group consisting of N, O, or S, and  
 wherein said ring is optionally substituted with R<sup>1</sup>;  
**R<sup>3</sup>** is selected from the group consisting of: substituted or  
 unsubstituted amidine, alkylamino, aminoalkyl, CONHR<sup>7</sup>, NH<sub>2</sub>,  
 NHCOR<sup>6</sup>, and CH<sub>2</sub>NHCOR<sup>6</sup>;
- 25 **R<sup>4</sup>** is selected from the group consisting of: halogen, alkylsulfinyl,  
 alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido,  
 hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl,  
 heteroaryl, and alkenyl, OR<sup>13</sup>, SR<sup>8</sup>, SO<sub>2</sub>N(R<sup>8</sup>)R<sup>8</sup>, NHR<sup>9</sup>, NHCOR<sup>9</sup>,  
 NR<sup>9</sup>COR<sup>9</sup>, NHCO(OR<sup>9</sup>), NR<sup>9</sup>CO(OR<sup>9</sup>), NR<sup>8</sup>SO<sub>2</sub>R<sup>10</sup>,  
 30 NHSO<sub>2</sub>N(R<sup>10</sup>)R<sup>10</sup>, NR<sup>6</sup>CON(R<sup>10</sup>)R<sup>10</sup>, COR<sup>9</sup>, CO<sub>2</sub>R<sup>8</sup>, CON(R<sup>8</sup>)R<sup>8</sup>,  
 wherein R<sup>8</sup> and R<sup>8</sup> may be taken together to form a 3-7 membered  
 carbocyclic ring having 1 to 3 substituted or unsubstituted

heteroatoms selected from S, SO, SO<sub>2</sub>, O, N, and NR<sup>6</sup>, and wherein R<sup>10</sup> and R<sup>10'</sup> may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO<sub>2</sub>, O, N, and NR<sup>6</sup> wherein said

5 aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R<sup>9</sup>;

R<sup>5</sup> is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl

10 are optionally substituted with one or more radicals selected from the group consisting of OR<sup>14</sup>, N(R<sup>14</sup>)R<sup>14'</sup>, and glycols;

R<sup>6</sup> is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl,

15 heterocyclicalkyl, and heterocyclic;

R<sup>7</sup> is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

20 R<sup>8</sup> is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R<sup>8'</sup> is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl,

25 heteroarylalkyl, and heterocyclicalkyl;

R<sup>9</sup> is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl,

30 aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with

one or more radical selected from the group consisting of:  
 alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl,  
 alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy,  
 halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl,  
 5 carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido,  
 benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate,  
 isothiocyanate, alkylldioxy, hydroxyalkyl, alkylamino,  
 alkylloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl,  
 alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally  
 10 substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and  
 alkylaminoalkyl;  
**R<sup>10</sup>** is independently selected from the group consisting of: hydrido,  
 lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino,  
 heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl,  
 15 heterocyclic, or arylalkyl are optionally substituted with one or more  
 radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano,  
 haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy,  
 benzyloxy, dialkylaminoalkyloxy, and heterocyclic,  
**R<sup>10'</sup>** is independently selected from the group consisting of: hydrido,  
 20 lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino,  
 heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl,  
 heterocyclic, or arylalkyl are optionally substituted with one or more  
 radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano,  
 haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy,  
 25 benzyloxy, dialkylaminoalkyloxy, and heterocyclic,  
**R<sup>11</sup>** is selected from the group consisting of: hydrido, halogen,  
 haloalkyl, CN, CO<sub>2</sub>R<sup>5</sup>, lower alkyl, lower alkenyl, lower alkynyl,  
 alkoxy, and CONH<sub>2</sub>;  
**R<sup>12</sup>** is selected from the group consisting of: hydrido, halogen, alkyl,  
 30 and alkoxy;  
**R<sup>13</sup>** is selected from the group consisting of: hydrido, alkyl, aryl,  
 arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein

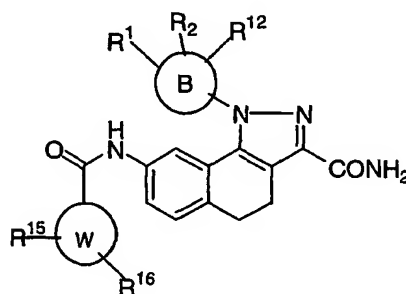
aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of  $OR^{14}$ ,  $N(R^{14})R^{14'}$ , and glycols;

$R^{14}$  is independently selected from the group consisting of hydrido, and lower alkyl; and

$R^{14'}$  is independently selected from the group consisting of hydrido, and lower alkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

Another class of compounds is defined by Formula III



wherein

B is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic wherein said aryl, heteroaryl, or heterocyclic are optionally substituted with  $R^1$ ,  $R^2$ , and  $R^{12}$ ;

W is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic;

$R^1$  is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN,  $NO_2$ ,  $OR^5$ ,

$OCOOR^5$ ,  $CO_2R^7$ ,  $CON(R^6)R^7$ ,  $COR^6$ ,  $SR^6$ ,  $SOR^6$ ,  $SO_2R^6$ ,  $NR^6R^7$ ,

$NR^6COR^7$ ,  $NR^6CONHR^7$ ,  $NR^6SO_2R^7$ ,  $NR^6SO_2NHR^7$ , and

$SO_2N(R^6)R^7$  wherein  $R^6$  and  $R^7$  may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted

heteroatoms selected from the group consisting of: S, SO, SO<sub>2</sub>, O, and NR<sup>6</sup>; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR<sup>5</sup> are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl, COCF<sub>3</sub>, CN, NO<sub>2</sub>, OR<sup>5</sup>, OCOOR<sup>5</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>6</sup>)R<sup>7</sup>, COR<sup>6</sup>, SR<sup>6</sup>, SOR<sup>6</sup>, SO<sub>2</sub>R<sup>6</sup>, NR<sup>6</sup>R<sup>7</sup>, NR<sup>6</sup>COR<sup>7</sup>, NR<sup>6</sup>CONHR<sup>7</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>6</sup>SO<sub>2</sub>NHR<sup>7</sup>, and SO<sub>2</sub>N(R<sup>6</sup>)R<sup>7</sup> wherein R<sup>6</sup> and R<sup>7</sup> may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO<sub>2</sub>, O, and NR<sup>6</sup>;

R<sup>2</sup> is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl, OR<sup>6</sup>, CN, NO<sub>2</sub>, SR<sup>6</sup>, NHR<sup>6</sup>, CON(R<sup>6</sup>)R<sup>7</sup>, NHCONHR<sup>6</sup>, CO<sub>2</sub>H, and haloalkyl;

R<sup>1</sup> and R<sup>2</sup> may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of N, O, or S, and wherein said ring is optionally substituted with R<sup>1</sup>;

R<sup>5</sup> is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of OR<sup>14</sup>, N(R<sup>14</sup>)R<sup>14</sup>, and glycols;

R<sup>6</sup> is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

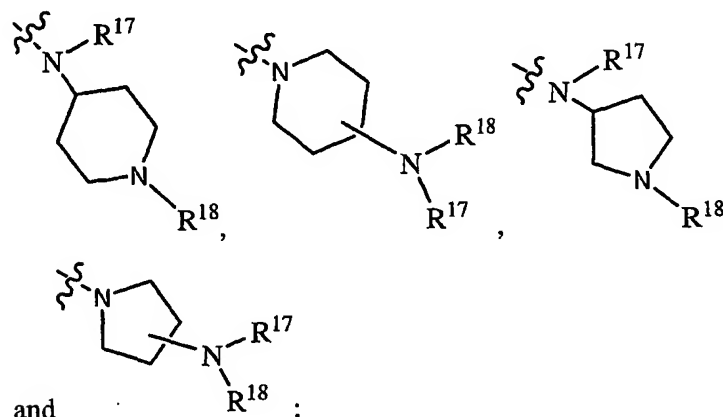
R<sup>7</sup> is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R<sup>12</sup> is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;

$R^{15}$  is selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl wherein said alkyl is optionally substituted with a carbocyclic or heterocyclic wherein said carbocyclic or heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(CH_2)_n C(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(CH_2)_n NHC(O)OR'$  wherein n is 0 to 4 and  $R'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl; alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkylldioxy, hydroxyalkyl, alkylamino, alkylloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic wherein said heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(CH_2)_n C(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein n is

0 to 4, and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl, (CH<sub>2</sub>)<sub>n</sub>NHC(O)OR' wherein n is 0 to 4 and R' is selected from the group consisting of hydrido, hydroxy, amino, and alkyl,

5



R<sup>17</sup> is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl; and

10

R<sup>18</sup> is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl;

15

20

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

25



## Definitions

[0018] The present invention includes the use of all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds, which releases the active parent drug according to Formula I, Formula II, or Formula III in vivo. If a chiral center or another form of an isomeric center is present in a compound of the present invention all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

[0019] The meaning of any substituent at any one occurrence in Formula I, Formula II or Formula III or any sub-Formula thereof is independent of its meaning, or any other substituents meaning, at any other occurrence, unless specified otherwise.

[0020] The term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the like. The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH<sub>2</sub>-)

radical. The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A

5 monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having

10 one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to

15 form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluoromethoxy. The term

20 "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane, and biphenyl. The term "heterocyclic" embraces saturated, partially saturated, and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and

25 oxygen. Examples of saturated heterocyclic radicals include pyrrolidyl and morpholinyl. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include thienyl, pyrrolyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, and tetrazolyl. The term also embraces radicals

30 where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The term "heterocyclic alkyl" embraces alkyl attached to the heterocyclic. The term

"sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals  $\text{--SO}_2\text{--}$ . "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The terms

5 "sulfamyl" or "sulfonamidyl", whether alone or used with terms such as "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl" and "N-alkyl-N-arylsulfamyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ( $\text{--SO}_2\text{--NH}_2$ ). The terms "N-alkylsulfamyl" and "N,N-dialkylsulfamyl" denote sulfamyl radicals substituted, respectively, with one alkyl

10 radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylsulfamyl" and "N-alkyl-N-arylsulfamyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes  $\text{--CO}_2\text{H}$ . The term "carboxyalkyl" embraces radicals having a carboxyl radical as defined

15 above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes  $\text{--(C=O)--}$ . The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is  $\text{CH}_3\text{--(C=O)--}$ . The term "alkylcarbonylalkyl" denotes an alkyl radical substituted with an "alkylcarbonyl"

20 radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl ( $\text{C=O}$ ) radical. Examples of such "alkoxycarbonyl" radicals include  $(\text{CH}_3)_3\text{CO--C=O--}$  and  $\text{--(O=C)OCH}_3$ . The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. Examples of such

25 "alkoxycarbonylalkyl" radicals include  $(\text{CH}_3)_3\text{COC(=O) (CH}_2)_2\text{--}$  and  $\text{--(CH}_2)_2\text{(O=C)OCH}_3$ . The term "amido" when used by itself or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical.

30 The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The terms "N-monoarylamido" and "N-alkyl-N-arylamido" denote

amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkyl radicals substituted with an N-alkyl-N-hydroxyamido radical. The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an  $-C(=NH)-NH_2$  radical. The term "cyanoamidino" denotes an  $-C(=N-CN)-NH_2$  radical. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, and diphenethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio,  $(CH_3-S-)$ . The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent  $-S(=O)-$  atom. The terms "N-alkylamino" and "N, N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino  $(CH_3C(=O)-NH-)$ .

[0021] Compounds of Formula I, Formula II or Formula III would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of

pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of Formula I, Formula II or Formula III would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondylo arthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, and juvenile arthritis.

5 Such compounds of Formula I, Formula II or Formula III would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns, and dermatitis. Compounds of Formula I, Formula II or Formula III also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable

10 bowel syndrome, and ulcerative colitis and for the prevention of colorectal cancer. Compounds of Formula I, Formula II or Formula III would be useful in treating inflammation in such diseases as vascular diseases such as vascularitis, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis,

15 nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds of the present invention may also be used for pain. The compounds are useful as antiinflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. The compounds

20 of Formula I, II or III are useful as agents for treating cancer or anticancer agents. The compounds of Formula I, II or III may be proapoptotic, antiapoptotic, anticell cycle progressive, antiinvasive, antiproliferative, antiangiogenic, and antimetastatic. The cancer may be colon, ovarian, breast, prostate, gastric, B-cell lymphoma, and multiple myeloma. More specifically, the compounds of this invention are useful in

25 the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic

30 leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias,

myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma. Due to the key role of PKs in the regulation of cellular proliferation, these compounds are also useful in the treatment of a variety of cell proliferative disorders such as, for instance, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis. The compounds of Formula I, II, or III may be used as an antiviral agent. The compounds of this invention are useful as inhibitors of protein kinases. The compounds of this invention are useful as inhibitors of IKK1 and/or IKK2, IKK $\alpha$ /IKK $\beta$  heterodimer, TBK or IKK $\gamma$ . The compounds of the invention may also be useful as inhibitors of other protein kinases such as, for instance, protein kinase C in different isoforms, cyclin dependent kinase (cdk), Met, PAK-4, PAK-5, ZC-1, STK-2, DDR-2, Aurora 1, Aurora 2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1, MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, VEGF-R, PI3K, weel kinase, Src, Abl, Akt, ILK, MK-2, IKK-2, Cdc7, Nek, and thus be effective in the treatment of diseases associated with other protein kinases. The present invention preferably includes compounds, which selectively inhibit IKK2 over IKK1. Preferably, the compounds have an IKK2 IC<sub>50</sub> of less than 1  $\mu$ M, and have a selectivity ratio of IKK2 inhibition over IKK1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have an IKK1 IC<sub>50</sub> of greater than 10  $\mu$ M, and more preferably of greater than 100  $\mu$ M. The compounds of Formula I, II, or III may also be used to treat angiogenesis associated cardiovascular, ophthalmology and osteoporosis disorders. The compounds of the present invention may also be used for treatment of knee injury such as sport injuries.

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[0022] While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation.

The present invention comprises a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention in association with at least one pharmaceutically acceptable carrier, adjuvant, or diluent. The present invention also comprises a method of treating inflammation or inflammation associated disorders in a subject, the method comprising administering to the subject having such inflammation or disorders a therapeutically effective amount of a compound of the present invention. Also included in the family of compounds of the present invention are the pharmaceutically acceptable salts thereof. The term "pharmaceutically acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of the present invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, salicylic, phydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic,  $\beta$ -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically acceptable base addition salts of compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methyl-glucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of the present invention by reacting, for example, the appropriate acid or base with the compound of the present invention.

[0023] Also embraced within this invention are pharmaceutical compositions comprising one or more compounds of the present invention in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants and/or excipient (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. Accordingly, the compounds of the present invention may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of the present invention prepared as herein before described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic aqueous solution. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, intravenously, subcutaneously, intramuscularly, intramedullary, orally, or topically. For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension, or liquid. The active ingredient may also be administered by injection as a composition wherein, for example, normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution may be used as a suitable carrier. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride, or sodium citrate. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound



employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg bodyweight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 1 to 20 mg/kg bodyweight, may be appropriate. The daily dose can be administered in one to four doses per day. For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered orally, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled release formulation as may be provided in a dispersion of active compound in a sustained release material such as glyceryl monostearate, glyceryl distearate, hydroxypropylmethyl cellulose alone or with a wax. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered orally or filled into a soft gelatin capsule. For rectal administration, the compounds of the present invention may also be combined with excipients such as cocoa butter, glycerin, gelatin, or polyethylene glycols and molded into a suppository. The methods of the

present invention include topical administration of the compounds of the present invention. By topical administration is meant non-systemic administration, including the application of a compound of the invention externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye, and nose, wherein the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal, and intramuscular administration. The amount of a compound of the present invention (hereinafter referred to as the active ingredient) required for therapeutic or prophylactic effect upon topical administration will, of course, vary with the compound chosen, the nature and severity of the condition being treated and the animal undergoing treatment, and is ultimately at the discretion of the physician.

[0024] The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carriers therefore, and optionally any other therapeutic ingredients. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of where treatment is required such as: liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.01 to 5.0 wt% of the formulation.

[0025] Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container, which is then sealed and sterilized by autoclaving, or maintaining at 90-100° C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are

phenylmercuric nitrate or acetate (0.00217c), benzalkonium chloride (0.0 1%) and chlorhexidine acetate (0.0 1%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol, and propylene glycol.

5     **[0026]**     Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or  
10     acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil. Creams, ointments, or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable  
15     machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogols. The formulation  
20     may incorporate any suitable surface-active agent such as an anionic, cationic, or non-ionic surface-active agent such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin may also be included. Other adjuvants and modes of administration are well  
25     and widely known in the pharmaceutical art. Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

#### GENERAL SYNTHETIC PROCEDURES

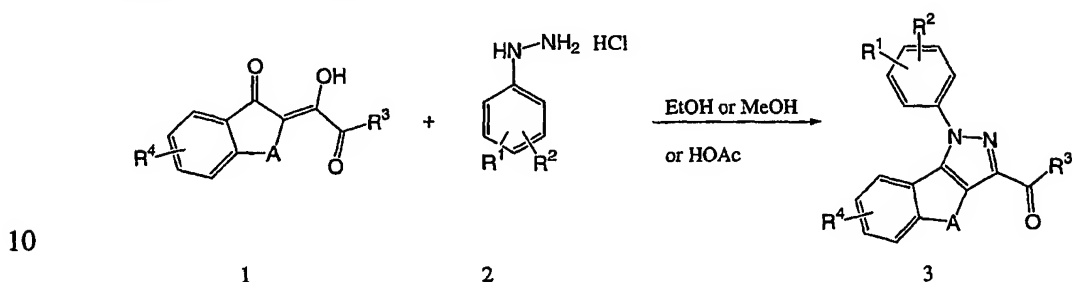
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**[0027]**     The starting materials used herein are commercially available or are prepared by routine methods well known to those of ordinary skill in the art and

can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

- 5 [0028] The compounds of the invention can be synthesized according to the following procedures of Schemes I-XI, wherein the  $R^1$ - $R^{14}$  substituents are as defined for Formula I, Formula II or Formula III, above, except where further noted.

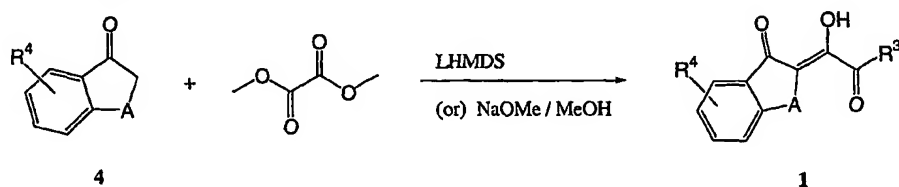
[0029] SCHEME I



Synthetic Scheme I illustrates the procedure used to prepare the antiinflammatory pyrazoles of the present invention. 1,3-Dicarbonyl compounds such as 1, or the shown enol form which is in equilibrium with the 1,3-diketone, are allowed to react with a substituted hydrazine hydrochloride 2 in warm methanol or ethanol or acetic acid to provide the pyrazoles 3 via a condensation reaction. When A =  $-\text{CH}_2\text{CH}_2-$ , the central ring may be aromatized to provide A =  $-\text{CH}=\text{CH}-$ , by using an oxidant such as DDQ, Pd or Pt on carbon with cyclooctadiene or other  $\text{H}_2$  acceptor, or sulfur in an appropriate solvent or without solvent.

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[0030] SCHEME II



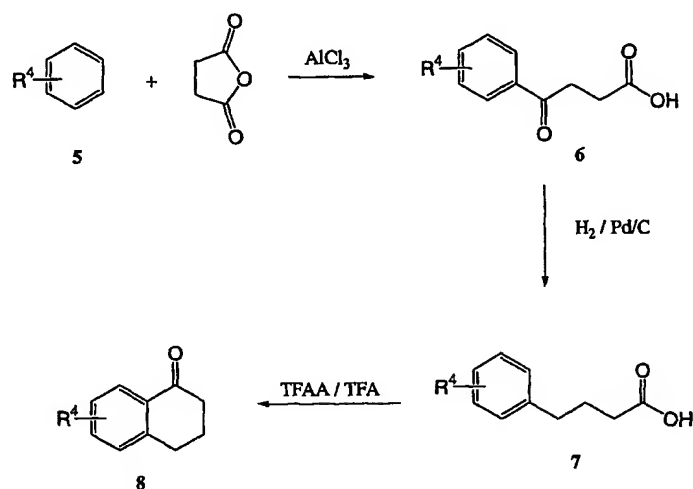
Synthetic Scheme II illustrates the procedure for the preparation of substituted diketones 1. An appropriately substituted ketone 4, including, but not limited to; 1-indanones, 1-tetralones, and 1-benzosuberones, is first treated with base, such as sodium methoxide, lithium bistrimethylsilylamide or lithium diisopropylamide

25

(LDA), followed by condensation with a suitable acylating agent, such as, dimethyl or diethyl oxalate, in an appropriate solvent, such as methanol, diethyl ether or tetrahydrofuran, to provide 1,3-dicarbonyl compounds 1 which are suitable for conversion into antiinflammatory pyrazoles as illustrated in Scheme I.

- 5 Alternatively, the dicarbonyl compounds 1 can be directly prepared from commercially available cyclic ketones 4.

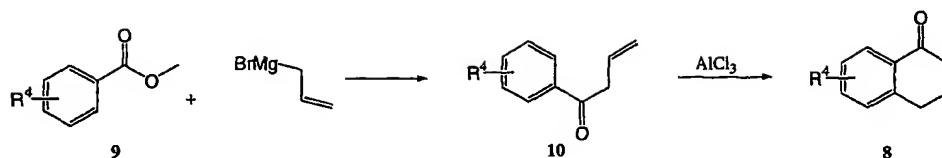
[0031] SCHEME III



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- Synthetic Scheme III illustrates a three-step procedure used for the preparation of substituted 1-tetralones. In step one, an appropriate substituted benzene 5 is condensed with succinic anhydride and a catalyst such as aluminum chloride into the corresponding 4-phenyl-4-ketobutanoic acid derivatives 6. In step two, the keto group of the 4-phenyl-4-ketobutanoic acids 6 is reduced using catalytic hydrogenation or Wolff-Kishner type reductions, thus providing 4-phenylbutanoic acids 7. In addition, ketone reductions can be carried out using metal amalgams. In step three, the 4-phenylbutanoic acids are treated with a mixture of trifluoroacetic anhydride, and trifluoroacetic acid to effect intramolecular Friedel-Crafts acylation affording selected tetralones 8. Alternatively, the Friedel-Crafts acylation can be affected with other strong acids such as polyphosphoric acid, sulfuric acid, or aluminum chloride.
- 15
- 20

## [0032] SCHEME IV

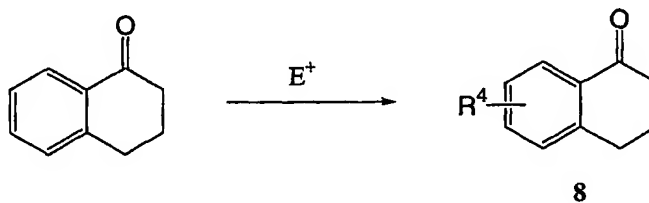


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Synthetic Scheme IV describes an alternate synthetic route to 1-tetralones 8. In step one, addition of allylmagnesium bromide in a suitable solvent such as, THF or diethyl ether, to an appropriately substituted benzoate 9 affords the 1-phenylbut-3-ene-1-ones 10. In step two, the 1-phenylbut-3-ene-1-ones 10 can be cyclized under Friedel-Crafts alkylation conditions, provided R<sup>4</sup> is a ring activating substituent, using catalysts such as aluminum chloride to produce 1-tetralones 8.

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## [0033] SCHEME V



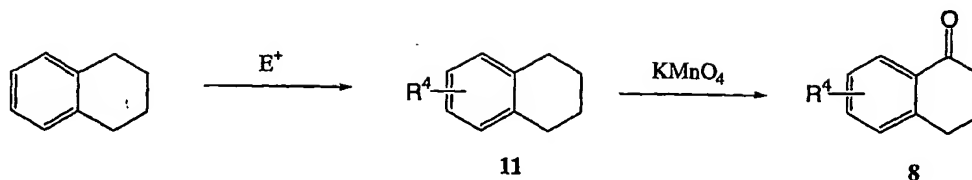
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Scheme V describes the direct modification of 1-tetralone to substituted tetralones. Commercially available 1-tetralone may be treated with a variety of electrophilic reagents such as bromine, ammonium nitrite or vinylsilanes, represented by E<sup>+</sup>, with or without a catalyst to generate directly a substituted tetralone 8, containing bromo, nitro or vinyl groups. Such tetralones 8 can be further embellished to provide the desired substitution patterns. Mixtures may be readily separated using chromatographic techniques.

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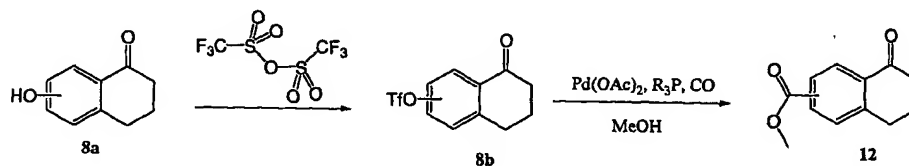
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## [0034] SCHEME VI



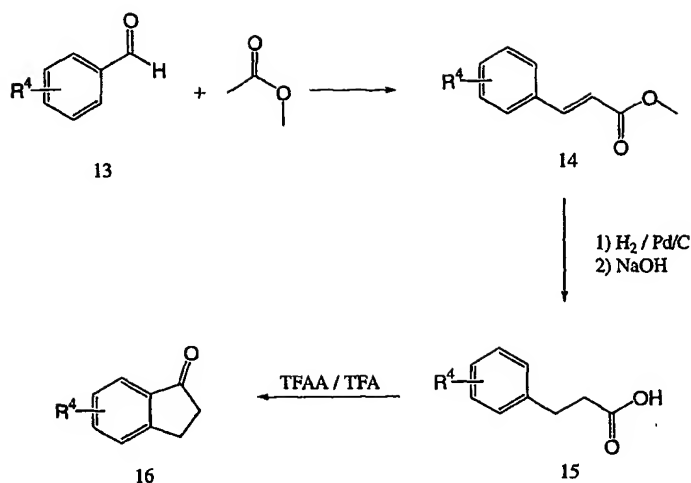
An alternate to Scheme V is Scheme VI wherein an appropriately substituted decaline is subjected to electrophilic addition to generate substituted decalins 11. Substituted decalins may also be prepared by Friedel-Crafts alkylation of substituted benzenes. Substituted decalins 11 can then be oxidized to the tetralones 8 using oxidants such as  $KMnO_4$  or  $SeO_2$ .

## 10 [0035] SCHEME VII



Scheme VII describes the modification of existing tetralones into analogs containing differing functional groups that can also be further modified. By example, hydroxy tetralone (8a where  $R_4 = OH$ ) can be converted to the triflate 8b by treatment with trifluoromethane sulfonyl anhydride. Triflate 8b can then be subjected to  $Pd(OAc)_2$ , an appropriate phosphine and CO in the presence of methanol to generate tetralone 12 containing a carboxy methyl group. Triflates can be used in a variety of palladium coupling reactions to introduce additional functional groups.

## [0036] SCHEME VIII

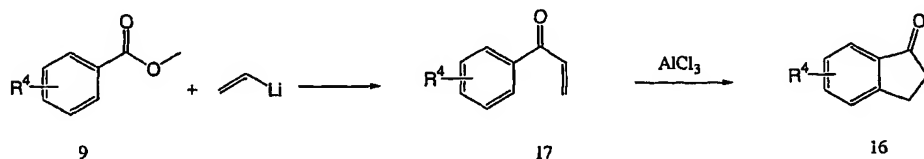


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Synthetic Scheme VIII illustrates a three step procedure used for the preparation of substituted 1-indanones 16. In step one, an appropriate substituted benzaldehyde 13 is condensed with methyl acetate and a catalyst such as triethylamine into the corresponding methyl cinnamate derivatives 14. Additionally, commercially available cinnamates may be used in the following steps. In step two the olefin group of the cinnamate 14 is reduced using catalytic hydrogenation and the ester hydrolyzed with base, such as NaOH, thus providing 3-phenylpropanoic acids 15. In step three, the 3-phenylpropanoic acids are treated with a mixture of trifluoroacetic anhydride and trifluoroacetic acid to effect intramolecular Friedel-Crafts acylation affording selected 1-indanones 16. Alternatively, the Friedel-Crafts acylation can be effected with other strong acids such as sulfuric acid or aluminum chloride.

## [0037] SCHEME IX

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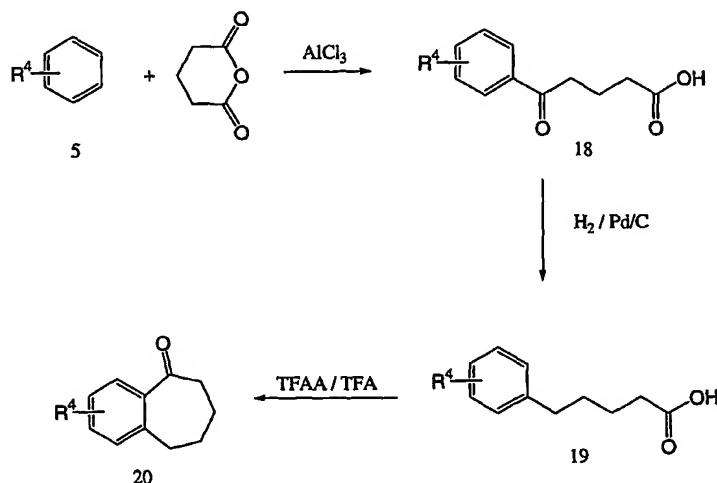


Synthetic Scheme IX illustrates a two-step route for the preparation of substituted 1-indanones 16. Commercially available methyl benzoates 9, or other alkyl esters, may be treated with a vinyl lithium reagent to afford phenylvinyl ketones 17.

- 5 Alternatively, dimethylamides or N-methyl-O-methylhydroxamides may be used in place of the esters. Also, other vinyl metals, such as; vinylmagnesium bromide may be used in place of the vinyl lithium reagent. The resulting phenylvinyl ketones may be cyclized using Friedel-Crafts alkylating catalysts, such as aluminum chloride.

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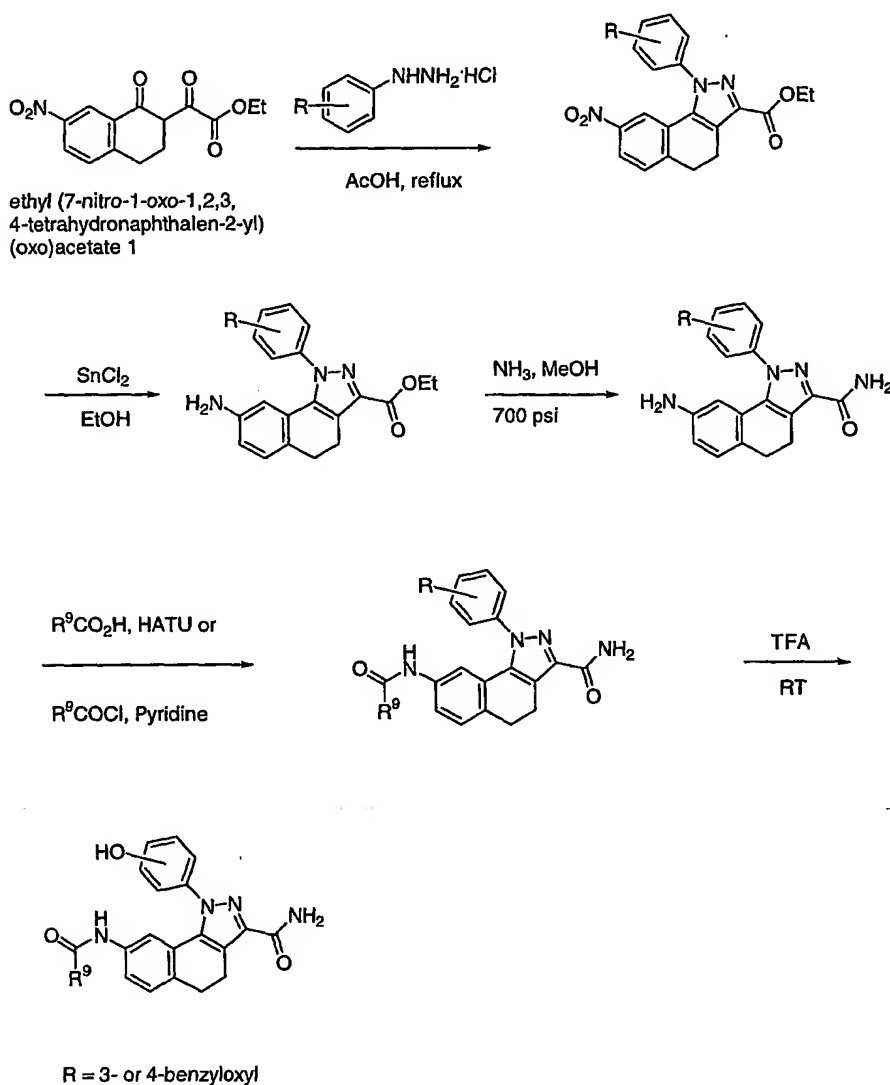
[0038] SCHEME X



- 15 Synthetic Scheme X illustrates a three step procedure used for the preparation of substituted 1-benzosuberones 20. In step one, an appropriate substituted benzene 5 is condensed with glutaric anhydride and a catalyst such as aluminum chloride into the corresponding 5-phenyl-5-ketopentanoic acid derivatives 18. In step two, the keto group of the 5-phenyl-5-ketopentanoic acids 18 is reduced using catalytic
- 20 hydrogenation or Wolff-Kishner type reductions, thus providing 5-phenylpentanoic acids 19. In addition, ketone reductions can also be carried out using metal amalgams. In step three, the 5-phenylpentanoic acids are treated with a mixture of trifluoroacetic anhydride, and trifluoroacetic acid to effect intramolecular Friedel-

Crafts acylation affording selected benzosuberones 20. Alternatively, the Friedel-Crafts acylation can be affected with other strong acids such as polyphosphoric acid,  $\text{H}_2\text{SO}_4$  or  $\text{AlCl}_3$ . Alternatively, 5-phenyl-5-ketopentanoic acids 18, can be prepared from glutaric acid and a phenyllithium or a phenyl Grignard reagent appropriately substituted and compatible with reaction conditions.

[0039] Scheme XI



Scheme XI describes the synthesis of the pyrazoles with phenols at N-position. In step one; 3- or 4-benzyloxyphenylhydrazine was refluxed with ethyl (7-nitro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)(oxo)acetate 1 in acetic acid to give pyrazole.

Then the nitro group was reduced to amine by using tin (II) chloride in ethanol. In the following step, the conversion of ester to amide was achieved by reacting with liquid ammonia in a pressured tube at high temperature. The resulting compound can either react with acid and HATU in DMF or acid chloride in pyridine to give the  
5 desired amide. The benzyl group was deprotected by stirring with TFA at room temperature.

[0040] The complete content of all publications, patents, and patent applications cited in this disclosure are herein incorporated by reference as if each individual  
10 publication, patent, or patent application were specifically and individually indicated to incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for the purposes of clarity of understanding, it will be readily apparent to one skilled in the art in light of the teachings of this invention that changes and modifications can be made  
15 without departing from the spirit and scope of the present invention. The following examples are provided for exemplification purposes only and are not intended to limit the scope of the invention, which has been described in broad terms above.

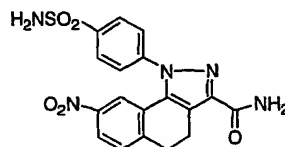
### EXAMPLES

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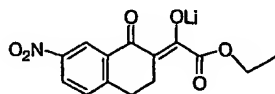
#### [0041] Example 1

1-{4-[(aminothio)peroxy]phenyl}-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

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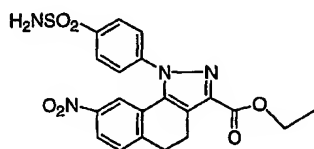
#### [0042] Step 1



To 7-nitro-1-tetralone (4.6 g, 0.024 mol) and ethyl oxalate (3.5 mL, 0.026 mol) in ether (100 mL) was added dropwise lithium bis(trimethylsilyl)amide (1M in THF, 26 mL). The slurry was stirred overnight and filtered to give the product as an olive green solid, 6.2 g (87% yield). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>/ 300 MHz) 8.45 (d, 1H); 8.05 (d of d, 1H); 7.42 (d, 1H); 4.08 (q, 2H); 2.82-2.72 (m, 2H); 2.51-2.43 (m, 2H); 1.21 (t, 3H).

[0043] Step 2

Ethyl 1-[4-[(aminothio)peroxy]phenyl]-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxylate



The material of Step 1 (6.2 g, 0.021 mol) and 4-sulfonamidophenylhydrazine hydrochloride (5.1 g, 0.023 mol) were stirred in methanol (100 mL) overnight. Conc. HCl (2 mL) was added to the thick slurry and the contents were heated on a steam bath for 1 hour. Contents were allowed to cool and filtered to give an off-white solid, 6.9 g. NMR and LC/MS analysis show the solid to contain two components, the desired and the hydrated pyrazole. TFA (60 mL) and TFAA (20 mL) were added to the solid and heated on a steam bath for 1 hour. Contents were concentrated *in vacuo* leaving the product as a solid, 6.4 g (69% yield). FABHRMS *m/z* 443.1020 (M+H, C<sub>20</sub>H<sub>19</sub>N<sub>4</sub>O<sub>6</sub>S requires 443.1025). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>/ 300 MHz) 8.10 (d of d, 1H); 8.03 (d, 2H); 7.82 (d, 2H); 7.70 (d, 1H); 7.62 (s, 1H); 7.50 (d, 1H); 4.33 (q, 2H); 3.20-2.95 (m, 4H); 1.33 (t, 3H).

25

Anal. Calcd for C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>O<sub>6</sub>S: C, 54.29; H, 4.10; N, 12.66. Found: C, 54.49; H, 4.00; N, 12.52.

[0044] Step 3

30

The material of Step 2 (718 mg, 0.0016 mol), conc. ammonium hydroxide (30 mL), and methanol (15 mL) were stirred in a stoppered flask for 72 hours. Contents were filtered to give a light amber solid (606 mg). The solid was recrystallized from acetonitrile to give the product as a light amber solid, 450 mg (68% yield).

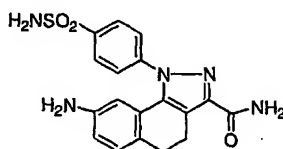
5 FABHRMS  $m/z$  414.0902 (M+H,  $C_{18}H_{16}N_5O_5S$  requires 414.0872).  $^1H$  NMR (DMSO- $d_6$  / 300 MHz) 8.15 - 7.95 (m, 3H); 7.83 (d, 2H); 7.80-7.40 (m, 6H); 3.20-2.95 (m, 4H).

Anal. Calcd for  $C_{18}H_{15}N_5O_5S$ : C, 52.30; H, 3.66; N, 16.94. Found: C, 52.04; H, 3.64; N, 16.61.

[0045] Example 2

8-amino-1-{4-[(aminothio)peroxy]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

15



The compound was prepared similarly to Example 1 in 70 % yield. FABHRMS  $m/z$  384.1136 (M+H,  $C_{18}H_{18}N_5O_3S$  requires 384.1130).  $^1H$  NMR (DMSO- $d_6$  / 300 MHz) 7.95 (d, 2H); 7.75 (d, 2H); 7.53 (br s, 1H); 7.43 (br s, 1H); 7.32 (br s, 1H); 7.01 (d, 1H); 6.44 (d of d, 1H); 6.03 (s, 1H); 4.81 (s, 2H); 2.93-2.65 (m, 4H).

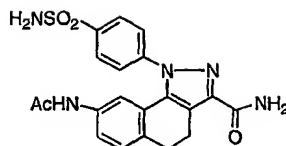
20

Anal. Calcd for  $C_{18}H_{17}N_5O_3S$ : C, 56.38; H, 4.47; N, 18.27. Found: C, 56.31; H, 4.42; N, 18.31.

25

[0046] Example 3

8-(acetylamino)-1-{4-[(aminothio)peroxy]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



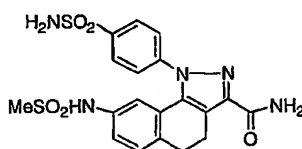
To the material of Example 2 (1.0 g, 0.0026 mol) in DMF (15 mL) was added dropwise a mixture of acetic anhydride (0.283 mL, 0.003 mol) and pyridine (0.243 mL, 0.003 mol) in DMF (5 mL). Contents were stirred overnight, diluted with water (75 mL), and filtered to give the desired as a white solid, 1.0 g (90% yield). FABHRMS  $m/z$  426.1235 ( $M+H$ ,  $C_{20}H_{20}N_5O_4S$  requires 426.1236).  $^1H$  NMR (DMSO- $d_6$  / 300 MHz) 9.80 (s, 1H); 8.00 (d, 2H); 7.75 (d, 2H); 7.60 (s, 1H); 7.48 (s, 2H); 7.39 (s, 1H); 7.30 (d, 1H); 7.15 (s, 1H); 2.90 (s, 4H); 1.92 (s, 3H).

10

Anal. Calcd for  $C_{20}H_{19}N_5O_4S$  ( $1H_2O$ ): C, 54.17; H, 4.77; N, 15.79. Found: C, 54.20; H, 4.97; N, 15.77.

#### [0047] Example 4

15 1-{4-[(aminothio)peroxy]phenyl}-8-[[[(methylthio)peroxy]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



20 To the material of Example 2 (1.2 g, 0.003 mol) and triethylamine (0.278 mL, 0.0035 mol) in DMF (10 mL) at 0°C, was added dropwise methanesulfonyl chloride (0.278 mL, 0.0035 mol) in  $CH_2Cl_2$  (2 mL). Contents were stirred overnight, slowly coming to room temperature. Contents were diluted with water (50 mL) and filtered to give the product as an off-white solid, 524 mg (37% yield). FABHRMS  $m/z$  462.0917 ( $M+H$ ,  $C_{19}H_{20}N_5O_5S_2$  requires 462.0906).  $^1H$  NMR (DMSO- $d_6$  / 300 MHz) 9.60 (s, 1H); 7.98 (d, 2H); 7.80 (d, 2H); 7.60 (s, 1H); 7.50 (s, 2H); 7.40 (s, 1H); 7.37 (d, 1H); 7.02 (s, 1H); 6.75 (s, 1H); 2.93 (s, 4H); 2.75 (s, 3H).

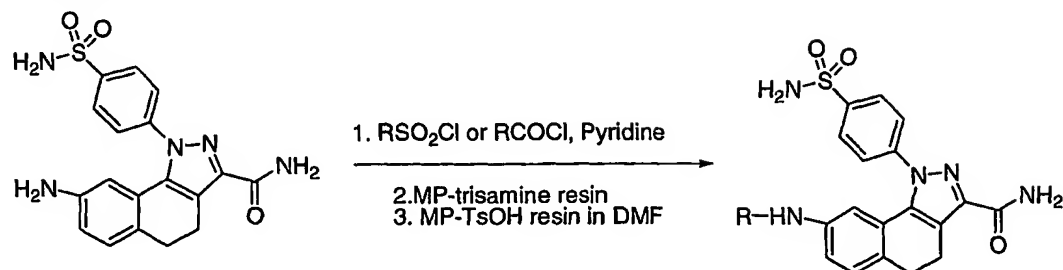
25

Anal. Calcd for  $C_{19}H_{19}N_5O_5S_2$ : C, 49.45; H, 4.15; N, 15.17. Found: C, 49.19; H, 3.77; N, 15.53.

5 [0048] Examples 5-40

Synthesis of the sulfonamide/amide/urea library

Scheme XII



10

The sulfonamides, amides, and urea were synthesized in a library format by using a Bohdan reaction block. The starting materials are the product of Example 2 (8-amino-1-(4-((aminiothio)peroxy)phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) and appropriate sulfonyl chlorides, acyl chlorides and isocyanates.

15 Thirty-five reactions constituted this library.

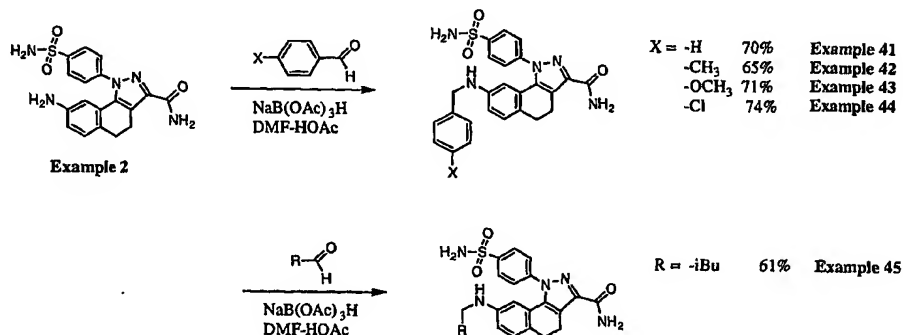
The general procedure is as follows: 48 mg of the product of Example 2 (8-amino-1-(4-((aminiothio)peroxy)phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) in 1 mL pyridine was placed in each reaction vessel, then 1.2 eq. of a sulfonyl chloride was added, and the mixture was shaken overnight. Then 3 mL methylene chloride and 300 mg of resin PS-trisamine were added, and then shaken over night. After filtration and washing with 2 mL methanol twice, the filtrates were combined and solvents evaporated. The residue was dissolved in 2 mL dimethylformamide, and MS-TsOH resin (450 mg) was added and shaken for 48 hours. After filtration and washing with 2 mL DMF, the combined filtrate was analyzed by LC-MS and LC. Then the filtrate was evaporated on a SpeedVac and the residue were suspended in 2 mL of  $H_2O/tBuOH$ , and lyophilized for 2 days. All compounds were obtained in solid form, and the majority of the compounds have about 90% purity. Table 1

shows the substitutions, compound identification, and IKK heterodimer assay values for the compounds from the sulfonamide library. The structures of the compounds of Examples 5-40 were confirmed Mass Spectroscopy and/or NMR analysis.

5

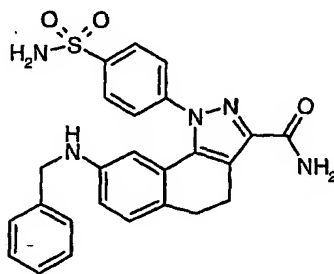
# [0049] Synthesis of Compounds of Examples 41-45

## Scheme XIII



# [0050] Example 41

1-[4-(aminosulfonyl)phenyl]-8-(benzylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



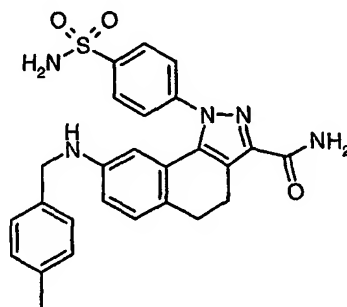
15 To a mixture of the product of example 2 (8-amino-1-{4-  
 [(aminiothio)peroxy]phenyl}-4,5-dihydro-1h-benzo[g]indazole-3-carboxamide) (76  
 mg, 0.20 mmol), acetic acid (0.3 mL) and sodium triacetoxyborohydride (213 mg,  
 1.00 mmol) in DMF (3 mL) was added benzaldehyde (64 mg, 0.60 mmol). The  
 resulted mixture was stirred at RT for 18 h, added water (10 mL), extracted with  
 20 EtOAc (3x10 mL). The combined organic layers was washed with water (3x10  
 mL), dried over MgSO<sub>4</sub>, filtered through a silica gel pad with EtOAc, and



concentrated. The crude product was triturated with diethyl ether to give 1-[4-(aminosulfonyl)phenyl]-8-(benzylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide as a yellow solid (66 mg, 70%). Its structure was confirmed by <sup>1</sup>H NMR and MS (474, M+1). C<sub>25</sub>H<sub>23</sub>N<sub>5</sub>O<sub>3</sub>S, Calc.: C: 63.41, H: 4.90, N: 14.79; Found, C: 63.11, H: 4.70, N: 13.54.

[0051] Example 42

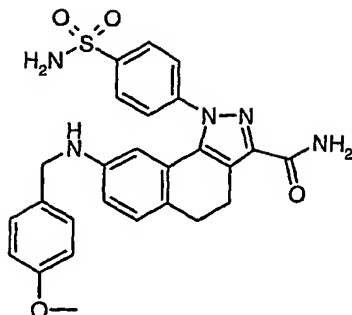
1-[4-(aminosulfonyl)phenyl]-8-[(4-methylbenzyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



1-[4-(aminosulfonyl)phenyl]-8-[(4-methylbenzyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (32 mg, 65%) was synthesized by the same procedure as in Example 41, starting with the product of Example 2 (8-amino-1-[4-[(aminiothio)peroxy]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (38.3 mg, 0.10 mmol) and *p*-Tolualdehyde (36 mg, 0.30 mmol). Its structure was confirmed by <sup>1</sup>H NMR and MS (488, M+1). C<sub>26</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub>S, Calc.: C: 64.05, H: 5.17, N: 14.36; Found, C: 63.78, H: 4.99, N: 14.12.

[0052] Example 43

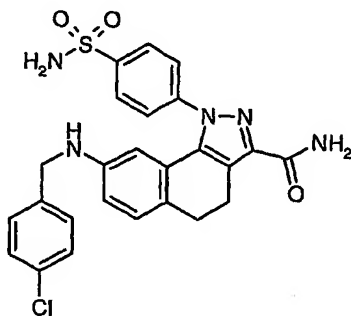
1-[4-(aminosulfonyl)phenyl]-8-[(4-methoxybenzyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



The title compound (36 mg, 71%) was synthesized by the same procedure as in Example 41 starting with the product of Example 2 (8-amino-1-{4-[(aminothio)peroxy]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (38.3 mg, 0.10 mmol) and *p*-anisaldehyde (38 mg, 0.30 mmol). Its structure was confirmed by <sup>1</sup>H NMR and MS (504, M+1). C<sub>26</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub>S.(Et<sub>2</sub>O)<sub>0.6</sub>, Calc.: C: 62.24, H: 5.70, N: 12.78; Found, C: 61.68, H: 5.43, N: 12.54.

[0053] Example 44

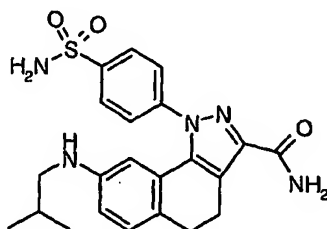
1-[4-(aminosulfonyl)phenyl]-8-[(4-chlorobenzyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



The title compound (37 mg, 74%) was synthesized by the same procedure as in Example 41 starting with the product of Example 2 (8-amino-1-{4-[(aminothio)peroxy]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (38.3 mg, 0.10 mmol) and *p*-chlorobenzaldehyde (42 mg, 0.30 mmol). Its structure was confirmed by <sup>1</sup>H NMR and MS (508, M+1). C<sub>25</sub>H<sub>22</sub>N<sub>5</sub>O<sub>3</sub>SCl, Calc.: C: 59.11, H: 4.37, N: 13.79; Found, C: 58.78, H: 4.25 N: 13.18.

**[0054] Example 45**

1-[4-(aminosulfonyl)phenyl]-8-(isobutylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

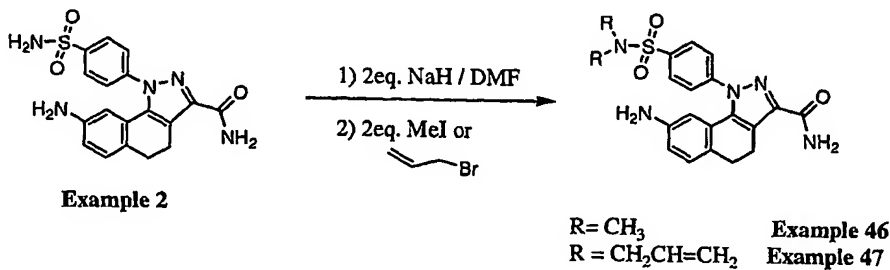


5

The title compound (27 mg, 61%) was synthesized by the same procedure as in Example 41 starting with the product of Example 2 (8-amino-1-{4-[(aminothio)peroxy]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (38.3 mg, 0.10 mmol) and isopropyl aldehyde (22 mg, 0.30 mmol). Its structure was confirmed by <sup>1</sup>H NMR and MS (440, M+1). C<sub>22</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub>S.H<sub>2</sub>O.(Et<sub>2</sub>O)<sub>0.2</sub>, Calc.: C: 57.97, H: 6.19, N: 14.83; Found, C: 57.63, H: 5.76 N: 14.04.

10

**[0055] Procedures for the synthesis of Compounds of Example 46 and 47**  
Scheme XIV

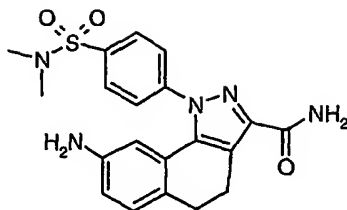


15

**[0056] Example 46**

8-amino-1-[4-[(dimethylamino)sulfonyl]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

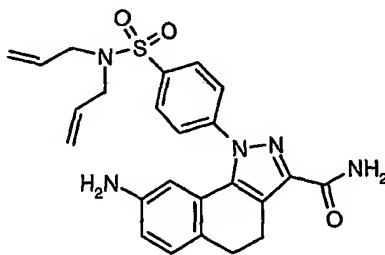
20



To a stirred solution of the product of Example 2 (8-amino-1-{4-  
 [(aminothio)peroxy]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (38  
 mg, 0.10 mmol) in DMF (1 mL) at RT under Ar was added sodium hydride in  
 5 mineral oil (60%, 8 mg, 0.20 mmol). After 2 h, iodomethane (28.4 mg, 0.20 mmol)  
 in DMF (1 mL) was added and the resulted mixture was stirred at RT for 18 h,  
 added water (10 mL), extracted with EtOAc (3x10 mL). The combined organic  
 layers was washed with water (3x10 mL), dried over MgSO<sub>4</sub>, filtered through a  
 silica gel pad with EtOAc, and concentrated. The crude product was triturated with  
 10 diethyl ether to give 8-amino-1-{4-[(dimethylamino)sulfonyl]phenyl}-4,5-dihydro-  
 1H-benzo[g]indazole-3-carboxamide as a yellow solid (29 mg, 70%). Its structure  
 was confirmed by <sup>1</sup>H NMR and MS (412, M+1). C<sub>20</sub>H<sub>21</sub>N<sub>5</sub>O<sub>3</sub>S.(H<sub>2</sub>O)<sub>0.3</sub>.(Et<sub>2</sub>O)<sub>0.3</sub>,  
 Calc.: C: 57.99, H: 5.65, N: 15.95; Found, C: 57.31, H: 5.18, N: 15.26.

15 [0057] Example 47

8-amino-1-{4-[(diallylamino)sulfonyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-  
 carboxamide

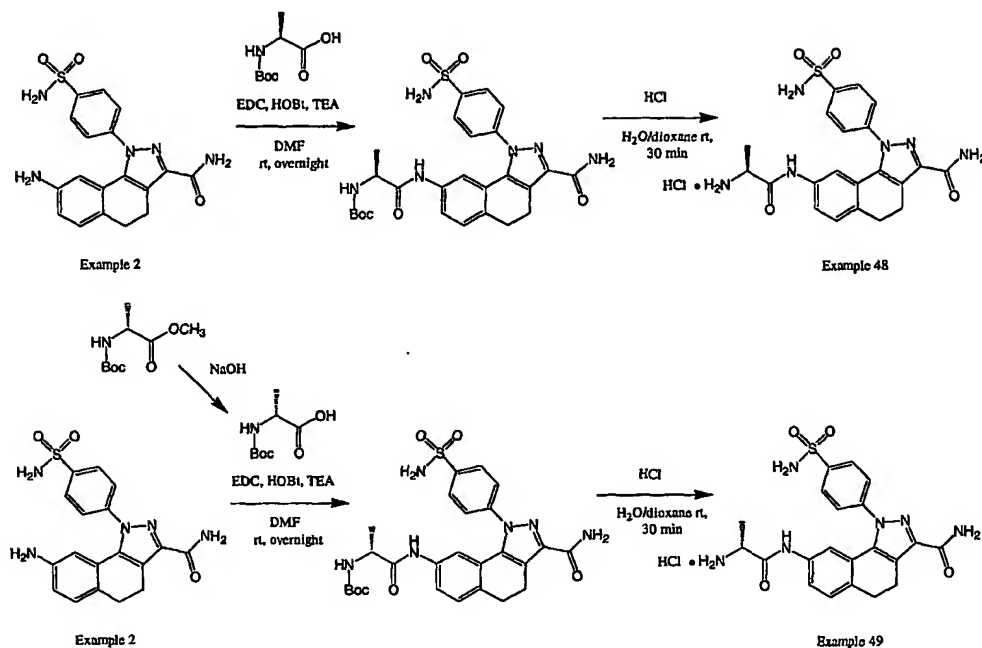


20 The title compound was synthesized by the same procedure used as for Example 46  
 except iodomethane was replaced by allyl bromide (24.2 mg, 0.20 mmol). The title  
 compound is a yellow solid (28 mg, 61%). Its structure was confirmed by <sup>1</sup>H NMR

and MS (464, M+1).  $C_{24}H_{25}N_5O_3S$ , Calc.: C: 62.18, H: 5.44, N: 15.11; Found, C: 61.76, H: 5.10, N: 14.77.

[0058] Synthesis of Examples 48 and 49

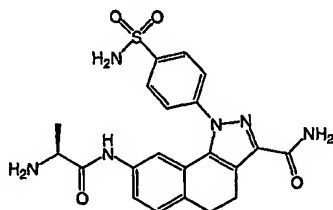
5 Scheme XV



[0059] Example 48

8-(L-alanyl-amino)-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

10

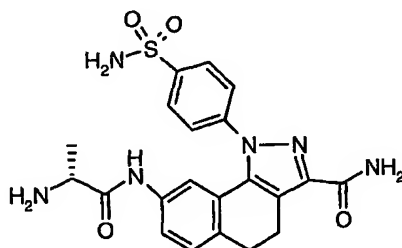


To a stirring solution of 8-amino-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (Example 2) (153 mg, 0.40 mmol) in DMF (6 mL) were added *N*-Boc-L-alanine (90 mg, 0.48 mmol), EDC (88 mg, 0.46 mmol), HOBT (60 mg, 0.44 mmol), and triethylamine (0.06 mL, 0.44 mmol). The reaction

5 mixture was allowed to stir overnight at room temperature. The DMF was then removed under reduced pressure and the resulting residue was purified by reverse phase preparative HPLC to give a beige powder (83 mg, 38 %). The powder was then dissolved in dioxane/water (2 mL, 1:1) and 5 M HCl (1 mL) was added at  
10 room temperature. After stirring for 3 hours, the solvent was removed under reduced pressure to give an oily residue. The residue was dissolved in a minimum amount of methanol and ether was added. The resulting precipitate was filtered to give the title compound as a pale yellow solid (66 mg, 90 %). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO): 1.33 (d, 3H, *J*= 6 Hz), 2.88-2.97 (m, 4H), 3.92 (m, 1H), 7.24-8.15 (7H, m); *M*+1=456, Anal. Calcd for C<sub>21</sub>H<sub>23</sub>N<sub>6</sub>O<sub>4</sub>SCl containing MeOH (1) and CH<sub>2</sub>Cl<sub>2</sub> (1): C, 45.44; H, 4.83; N, 13.82. Found C, 45.37; H, 4.83; N, 13.60.

[0060] Example 49

15 8-(D-alanyl-amino)-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



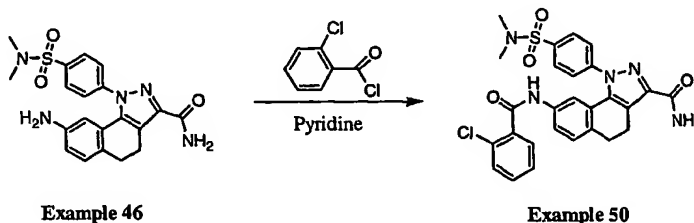
20 To a stirring solution of 8-amino-1-[4-[(aminiothio)peroxy]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (Example 2) (156 mg, 0.40 mmol) in DMF (6 mL) were added *N*-Boc-D-alanine (81 mg, 0.43 mmol), EDC (85 mg, 0.44 mmol), HOBT (58 mg, 0.43 mmol), and triethylamine (0.06 mL, 0.44 mmol). The reaction mixture was allowed to stir overnight at room temperature. The DMF was then removed under reduced pressure and the resulting residue was purified by reverse  
25 phase preparative HPLC to give a beige powder (122 mg, 56 %). The powder was then dissolved in dioxane/water (2 mL, 1:1) and 5 M HCl (1 mL) was added at room temperature. After stirring for 3 hours, the solvent was removed under

reduced pressure to give the title compound as a light orange solid (92 mg, 87 %).

$^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO): 1.35 (d, 3H,  $J = 6$  Hz), 2.80-2.94 (m, 4H), 3.91 (m, 1H), 7.13-8.14 (7H, m);  $M+1=456$ .

## 5 [0061] Example 50

8-[(2-chlorobenzoyl)amino]-1-{4-[(dimethylamino)sulfonyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



10

To a stirred solution of 8-amino-1-{4-[(dimethylamino)sulfonyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (Example 46) (1.52 g, 3.70 mmol) in pyridine (25 mL) at RT was added 2-chlorobenzoyl chloride (970 mg, 5.55 mmol). After 14 h, triamine (1 g) was added and the mixture was stirred for 2 h. The mixture was filtered through a silica gel pad with EtOAc and concentrated. Column chromatography (silica gel, EtOAc) gave the title compound as a yellow solid (900 mg, 1.63 mmol, 44%). Its structure was confirmed by  $^1\text{H}$  NMR and MS (551,  $M+1$ ).  $\text{C}_{27}\text{H}_{24}\text{ClN}_5\text{O}_4\text{S}$ , Calc.: C: 58.96, H: 4.40, N: 12.73; Found, C: 58.66, H: 4.65, N: 12.58.

20

## [0062] Examples 51-91

Synthesis of the sulfonamide/amide/urea library

The sulfonamides, amides, and ureas of Examples 51-91 were synthesized in a library format as described in Examples 5-40. The starting materials are the product of Example 4 (8-amino-1-{4-[(aminothio)peroxy]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) and appropriate sulfonyl chlorides, acyl chlorides and isocyanates. Table 1 shows the compound identification, compound, IKK resin

assay values, formula weight, and mass spectroscopy characterization for the compounds from the library.

Table 1

COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 1	> 100 μM	413.41	414
8-amino-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 2	≤1 μM	383.43	384
8-(acetylamino)-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 3	10 ≤ 100 μM)	425.47	426
1-[4-(aminosulfonyl)phenyl]-8-[(methylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 4	≤1 μM	461.52	462
1-[4-(aminosulfonyl)phenyl]-8-[[trifluoromethyl)sulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 5	10 ≤ 100 μM	515.49	516
1-[4-(aminosulfonyl)phenyl]-8-[(ethylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 6	≤1 μM	475.55	478



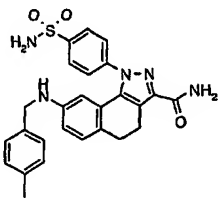
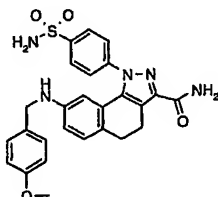
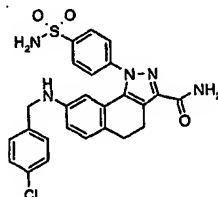
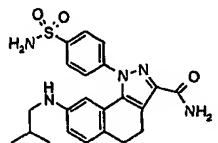
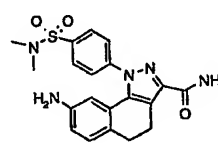
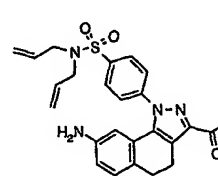
COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8- {[(2,2,2-trifluoroethyl)sulfonyl]amino}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 7	1 ≤ 10 μM	529.52	530
1-[4-(aminosulfonyl)phenyl]-8- [(propylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 8	1 ≤ 10 μM	489.58	490
1-[4-(aminosulfonyl)phenyl]-8- [(isopropylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 9	1 ≤ 10 μM	489.58	490
1-[4-(aminosulfonyl)phenyl]-8- [(butylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 10	1 ≤ 10 μM)	503.60	531
1-[4-(aminosulfonyl)phenyl]-8- [(benzylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 11	1 ≤ 10 μM)	537.62	538
1-[4-(aminosulfonyl)phenyl]-8- [(1-naphthylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 12	10 ≤ 100 μM	573.65	574
1-[4-(aminosulfonyl)phenyl]-8- {[(5-(dimethylamino)-1-naphthyl)sulfonyl]amino}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 13	1 ≤ 10 μM	616.72	617

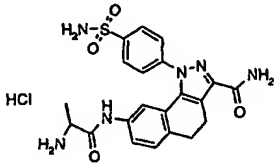
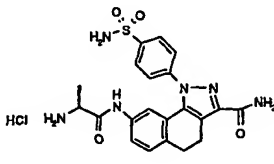
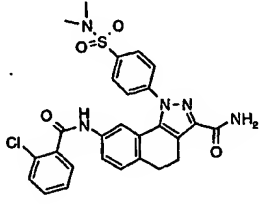
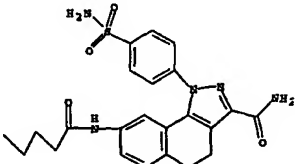
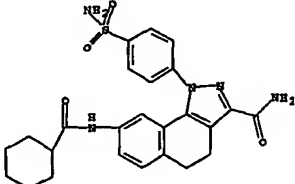
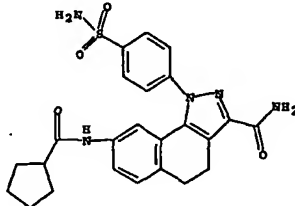
COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8-[[isoquinolin-5-ylsulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 14	1 ≤ 10 μM	574.64	575
1-[4-(aminosulfonyl)phenyl]-8-[[quinolin-7-ylsulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 15	> 100 μM	574.64	575
1-[4-(aminosulfonyl)phenyl]-8-[[2,1,3-benzoxadiazol-4-ylsulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 16	1 ≤ 10 μM	565.59	575
1-[4-(aminosulfonyl)phenyl]-8-[[1,1'-biphenyl-4-ylsulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 17	1 ≤ 10 μM	599.69	600
1-[4-(aminosulfonyl)phenyl]-8-[[5-(pyridin-2-ylthien-2-yl)sulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 18	10 ≤ 100 μM	606.71	607
1-[4-(aminosulfonyl)phenyl]-8-[[1-methyl-1H-imidazol-4-yl)sulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 19	10 ≤ 100 μM	527.58	528
1-[4-(aminosulfonyl)phenyl]-8-[[1,2-dimethyl-1H-imidazol-4-yl)sulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 20	10 ≤ 100 μM	541.61	542

COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
8-([2-(acetylamino)-4-methyl-1,3-thiazol-5-yl]sulfonyl)amino)-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 21	1 ≤ 10 μM	601.69	602
1-[4-(aminosulfonyl)phenyl]-8-(((4-methylphenyl)sulfonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 22	10 ≤ 100 μM 3)	537.62	538
1-[4-(aminosulfonyl)phenyl]-8-(((4-methoxyphenyl)sulfonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 23	10 ≤ 100 μM	553.62	554
1-[4-(aminosulfonyl)phenyl]-8-(((4-fluorophenyl)sulfonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 24	1 ≤ 10 μM	541.58	542
1-[4-(aminosulfonyl)phenyl]-8-(((4-chlorophenyl)sulfonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 25	1 ≤ 10 μM	558.04	559
1-[4-(aminosulfonyl)phenyl]-8-(((4-bromophenyl)sulfonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 26	1 ≤ 10 μM	602.49	603
1-[4-(aminosulfonyl)phenyl]-8-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 27	10 ≤ 100 μM	591.59	592

COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8- {[(3,4-dichlorophenyl)sulfonyl]a mino}-4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 28	1 ≤ 10 μM	592.48	593
1-[4-(aminosulfonyl)phenyl]-8- {[(2,5-dichlorophenyl)sulfonyl]a mino}-4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 29	1 ≤ 10 μM	592.48	593
1-[4-(aminosulfonyl)phenyl]-8- {[(2,4-dichlorophenyl)sulfonyl]a mino}-4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 30	1 ≤ 10 μM	592.48	593
1-[4-(aminosulfonyl)phenyl]-8- {[(2,4-difluorophenyl)sulfonyl]a mino}-4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 31	10 ≤ 100 μM	559.57	560
1-[4-(aminosulfonyl)phenyl]-8- {[(3,4-difluorophenyl)sulfonyl]a mino}-4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 32	10 ≤ 100 μM	559.57	560
1-[4-(aminosulfonyl)phenyl]-8- {[(4-bromo-2-fluorophenyl)sulfonyl]a mino}-4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 33	1 ≤ 10 μM	620.48	621
1-[4-(aminosulfonyl)phenyl]-8- {[(3,4-dimethoxyphenyl)sulfonyl] amino}-4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 34	10 ≤ 100 μM	583.64	584

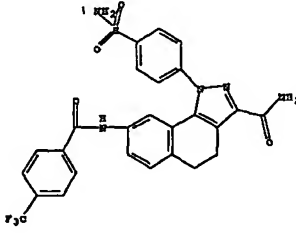
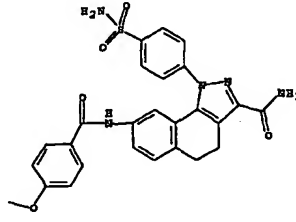
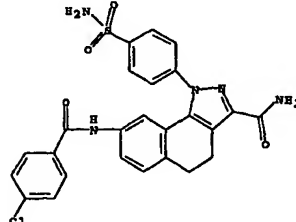
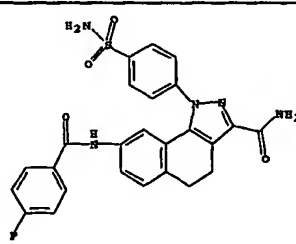
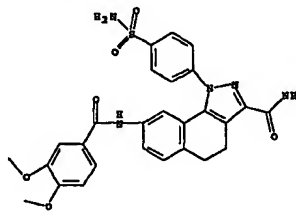
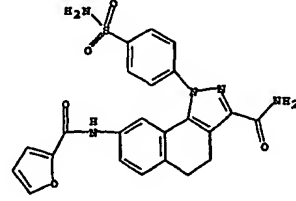
COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8- {[3,5-bis(trifluoromethyl)phenyl] sulfonyl}amino)-4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 35	1 ≤ 10 μM	659.59	660
1-[4-(aminosulfonyl)phenyl]-8- {[(2,4,5-trichlorophenyl)sulfonyl]a mino)-4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 36	1 ≤ 10 μM	626.93	627
1-[4-(aminosulfonyl)phenyl]-8- (propionylamino)-4,5- dihydro-1H- benzo[g]indazole-3- carboxamide		Example 37	1 ≤ 10 μM	439.49	440
1-[4-(aminosulfonyl)phenyl]-8- (benzoylamino)-4,5- dihydro-1H- benzo[g]indazole-3- carboxamide		Example 38	1 ≤ 10 μM	487.54	489
1-[4-(aminosulfonyl)phenyl]-8- {[(ethylamino)carbonyl]a mino)-4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 39	1 ≤ 10 μM	454.51	455
1-[4-(aminosulfonyl)phenyl]-8- [(anilino)carbonyl]amino)- 4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 40	1 ≤ 10 μM	502.55	503
1-[4-(aminosulfonyl)phenyl]-8- (benzylamino)-4,5- dihydro-1H- benzo[g]indazole-3- carboxamide		Example 41	1 ≤ 10 μM	473.56	474

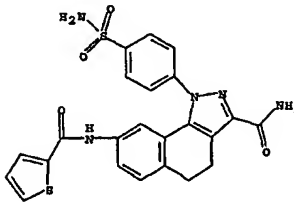
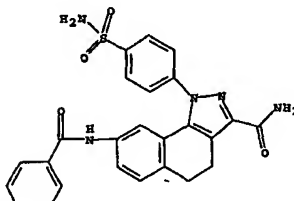
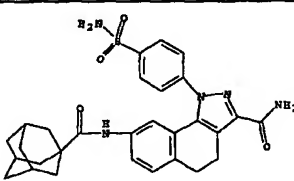
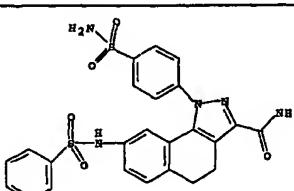
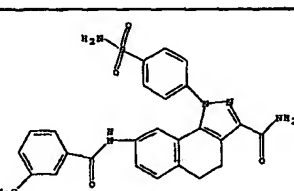
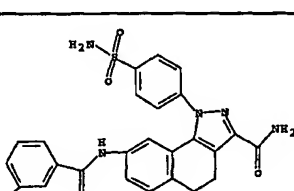
COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8-[(4-methylbenzyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 42	10 ≤ 100 μM	487.58	488
1-[4-(aminosulfonyl)phenyl]-8-[(4-methoxybenzyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 43	1 ≤ 10 μM	503.58	
1-[4-(aminosulfonyl)phenyl]-8-[(4-chlorobenzyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 44	10 ≤ 100 μM	508.00	509
1-[4-(aminosulfonyl)phenyl]-8-(isobutylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 45	10 ≤ 100 μM	439.54	440
8-amino-1-[4-[(dimethylamino)sulfonyl]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 46	1 ≤ 10 μM	411.48	412
8-amino-1-[4-[(diallylamino)sulfonyl]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 47	1 ≤ 10 μM	463.56	464

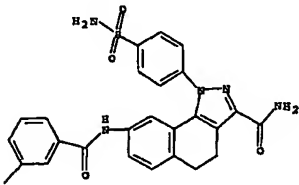
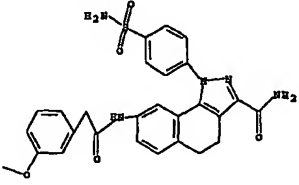
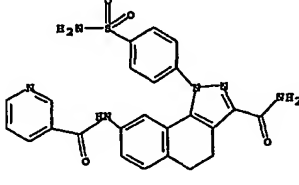
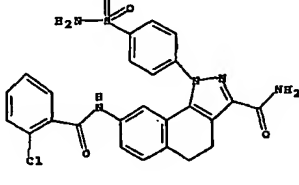
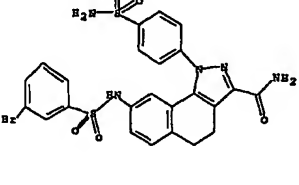
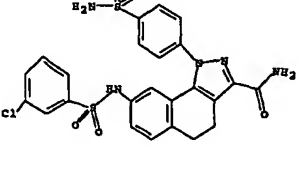
COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
8-(L-alanylamino)-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride		Example 48	1 ≤ 10 μM	490.97	492
8-(D-alanylamino)-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride		Example 49	1 ≤ 10 μM	490.97	492
8-[(2-chlorobenzoyl)amino]-1-[4-[(dimethylamino)sulfonyl]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 50	≤1 μM	550.04	551
1-[4-(aminosulfonyl)phenyl]-8-(pentanoylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 51	1 ≤ 10 μM	467.55	467
1-[4-(aminosulfonyl)phenyl]-8-[(cyclohexylcarbonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 52	1 ≤ 10 μM	493.59	494
1-[4-(aminosulfonyl)phenyl]-8-[(cyclopentylcarbonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 53	1 ≤ 10 μM	470.56	480

COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8-[(cyclobutylcarbonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 54	1 ≤ 10 μM	465.53	466
1-[4-(aminosulfonyl)phenyl]-8-[(cyclopropylcarbonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 55	1 ≤ 10 μM	451.51	452
1-[4-(aminosulfonyl)phenyl]-8-(butyrylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 56	1 ≤ 10 μM	453.52	454
1-[4-(aminosulfonyl)phenyl]-8-[(phenylacetyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 57	1 ≤ 10 μM	501.57	502
1-[4-(aminosulfonyl)phenyl]-8-[(methoxyacetyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 58	1 ≤ 10 μM	455.49	456
1-[4-(aminosulfonyl)phenyl]-8-(isobutyrylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 59	1 ≤ 10 μM	453.52	454

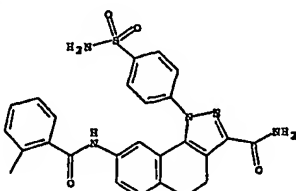
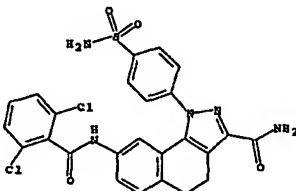
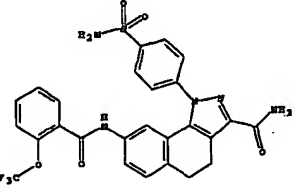
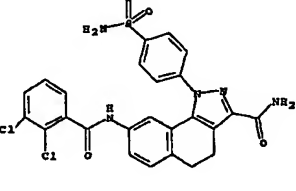
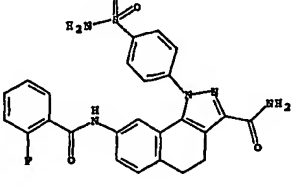
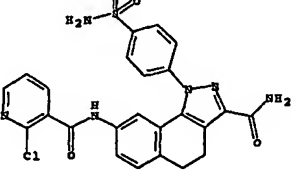


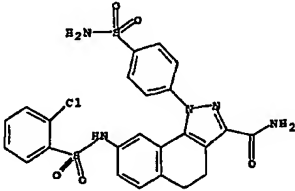
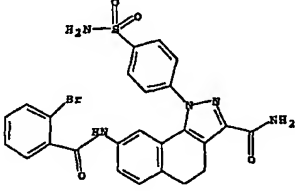
COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8- {[4-(trifluoromethyl)benzoyl]a mino}-4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 60	1 ≤ 10 μM	555.54	556
1-[4-(aminosulfonyl)phenyl]-8- [(4-methoxybenzoyl)amino]- 4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 61	≤1 μM	517.56	518
1-[4-(aminosulfonyl)phenyl]-8- [(4-chlorobenzoyl)amino]- 4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 62	≤1 μM	521.98	522
1-[4-(aminosulfonyl)phenyl]-8- [(4-fluorobenzoyl)amino]- 4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 63	≤1 μM	505.53	506
1-[4-(aminosulfonyl)phenyl]-8- [(3,4-dimethoxybenzoyl)amino]- 4,5-dihydro-1H- benzo[g]indazole-3- carboxamide		Example 64	1 ≤ 10 μM	547.59	548
1-[4-(aminosulfonyl)phenyl]-8- (2-furoylamino)-4,5- dihydro-1H- benzo[g]indazole-3- carboxamide		Example 65	10 ≤ 100 μM	477.5	478

COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8-[(thien-2-ylcarbonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 66	10 ≤ 100 μM	493.57	494
1-[4-(aminosulfonyl)phenyl]-8-(isonicotinoylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 67	≤1 μM	488.53	489
8-[(1-adamantylcarbonyl)amino]-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 68	1 ≤ 10 μM	545.66	546
1-[4-(aminosulfonyl)phenyl]-8-[(phenylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 69	1 ≤ 10 μM	523.59	526
1-[4-(aminosulfonyl)phenyl]-8-[[3-(trifluoromethyl)benzoyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 70	1 ≤ 10 μM	555.54	556
1-[4-(aminosulfonyl)phenyl]-8-[[3-methylbenzoyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 71	≤1 μM	501.57	502

COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8-[(3-bromobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 72	≤1 μM	566.43	567
1-[4-(aminosulfonyl)phenyl]-8-[[3-methoxyphenyl)acetyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 73	1 ≤ 10 μM	531.59	532
1-[4-(aminosulfonyl)phenyl]-8-[(pyridin-3-ylcarbonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 74	≤1 μM	488.53	489
1-[4-(aminosulfonyl)phenyl]-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 75	≤1 μM	521.98	522
1-[4-(aminosulfonyl)phenyl]-8-[[3-bromophenyl)sulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 76	1 ≤ 10 μM	602.49	603
1-[4-(aminosulfonyl)phenyl]-8-[[3-chlorophenyl)sulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 77	1 ≤ 10 μM	558.04	559

COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8-[(3-cyanobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 78	$\leq 1$ $\mu\text{M}$	512.55	513
1-[4-(aminosulfonyl)phenyl]-8-[[3-(3-methylphenyl)sulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 79	$10 \leq$ $100$ $\mu\text{M}$	537.62	538
1-[4-(aminosulfonyl)phenyl]-8-[(3-methoxybenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 80	$\leq 1$ $\mu\text{M}$	517.56	518
1-[4-(aminosulfonyl)phenyl]-8-[(3-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 81	$\leq 1$ $\mu\text{M}$	521.98	522
1-[4-(aminosulfonyl)phenyl]-8-[(2-methoxybenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 82	$10 \leq$ $100$ $\mu\text{M}$	517.56	518
1-[4-(aminosulfonyl)phenyl]-8-[[2-(trifluoromethyl)benzoyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 83	$\leq 1$ $\mu\text{M}$	555.54	556

COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8-[(2-methylbenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 84	≤1 μM	501.57	502
1-[4-(aminosulfonyl)phenyl]-8-[(2,6-dichlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 85	≤1 μM	556.43	557
1-[4-(aminosulfonyl)phenyl]-8-[(2-(trifluoromethoxy)benzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 86	≤1 μM	571.53	572
1-[4-(aminosulfonyl)phenyl]-8-[(2,3-dichlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 87	≤1 μM	556.43	557
1-[4-(aminosulfonyl)phenyl]-8-[(2-fluorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 88	≤1 μM	505.53	506
1-[4-(aminosulfonyl)phenyl]-8-[[2-(2-chloropyridin-3-yl)carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 89	≤1 μM	522.97	523

COMPOUND	STRUCTURE	EXAMPLE	IKK2 -resin	Formula Weight	Mass Spec
1-[4-(aminosulfonyl)phenyl]-8-[[[(2-chlorophenyl)sulfonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 90	$10 \leq 100$ $\mu\text{M}$	558.04	558
1-[4-(aminosulfonyl)phenyl]-8-[[[(2-bromobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide		Example 91	$\leq 1$ $\mu\text{M}$	566.43	567

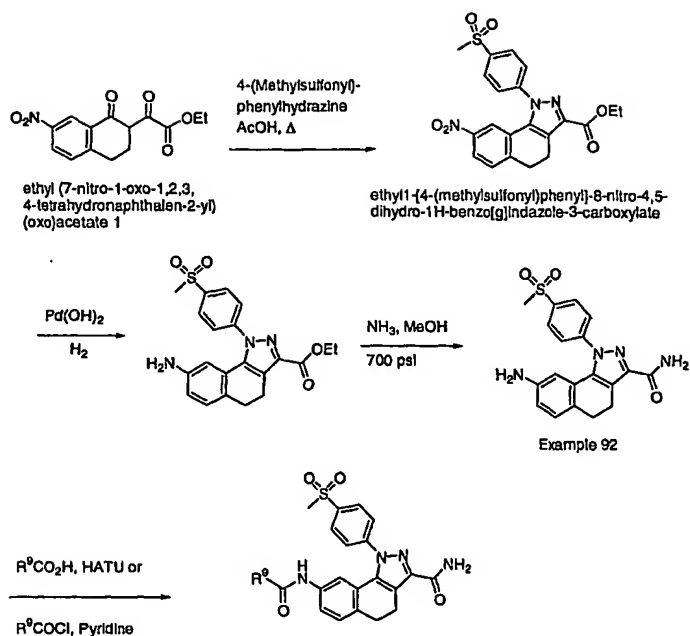
[0063] Examples 92-125

[0064] Examples 92-125 shown in Table 2 were synthesized using the

following synthesis procedure similar to scheme I where  $R^9$  is the appropriate aryl,

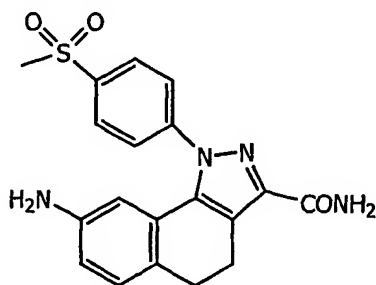
5 substituted aryl, heteroaryl, substituted heteroaryl, substituted arylalkyl, substituted heteroarylalkyl, or cycloalkyl.

Scheme XV

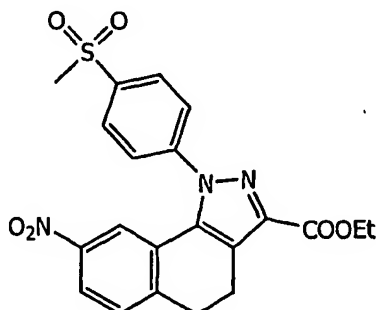


## [0065] Example 92

5 8-amino-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride



## [0066] Step 1

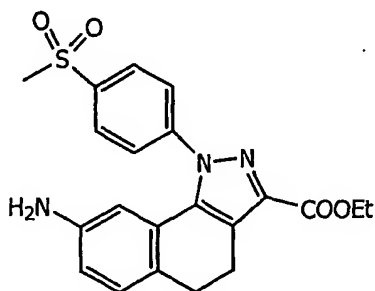


10 A mixture of (17.2 mmoles) of diketo ester and (17.2 mmoles) 4-(Methylsulfonyl)-

phenylhydrazine in 100ml of acetic acid was refluxed with stirring for 3h, and then cooled. The mixture was concentrated, and the residue triturated with ethyl acetate affording a brown solid, which was filtered, washed with ethyl acetate, and dried to give the title compound. The structure was supported by  $^1\text{H}$  NMR.

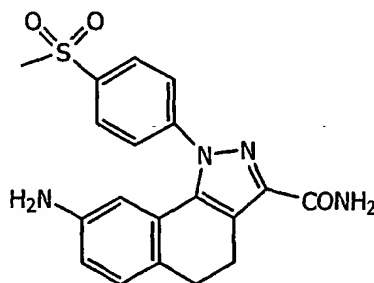
5

[0067] Step 2



A solution of the title product of Step 1 in acetic acid was treated at room temperature with 5% palladium on carbon under an atmosphere of hydrogen gas at 5 psi. The reaction was followed by LC-MS. When the conversion was complete, the mixture was filtered and concentrated to give the title compound as a brownish oil that was used directly for the next step.

[0068] Step 3  
8-amino-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride



The title product of Step 2 was dissolved in anhydrous ethanol and then an approximately equal volume of liquid ammonia was added. The resulting mixture was sealed in a pressure vessel and then stirred overnight at 100°C. After cooling, the mixture was concentrated. The residue was taken up in dichloromethane –

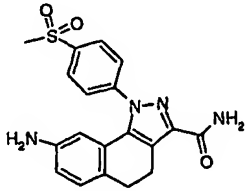
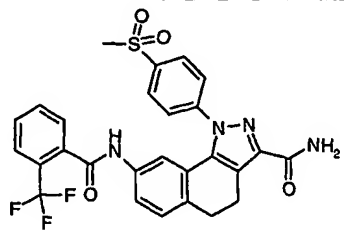
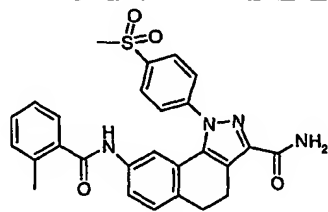
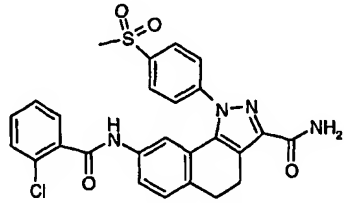
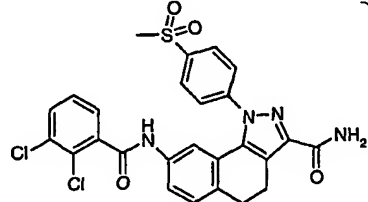
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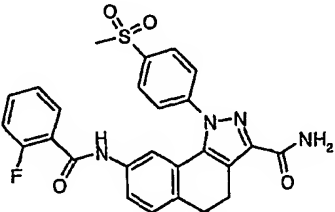
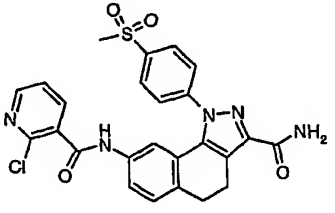
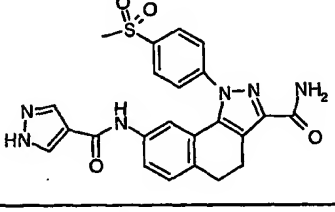
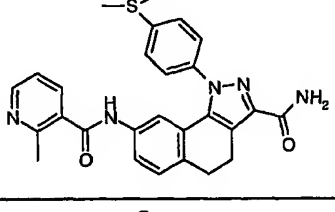
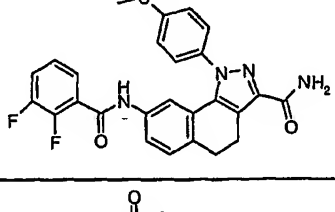
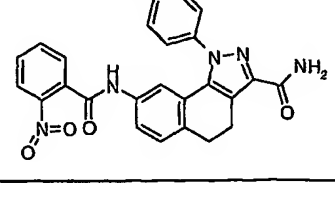


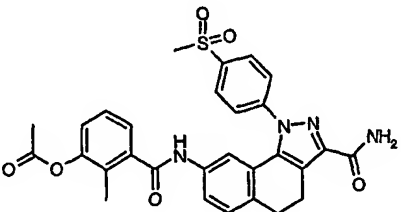
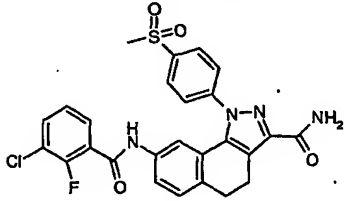
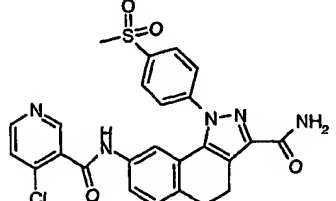
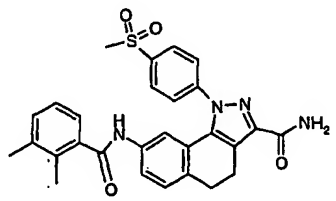
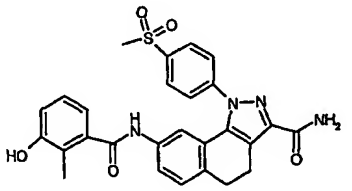
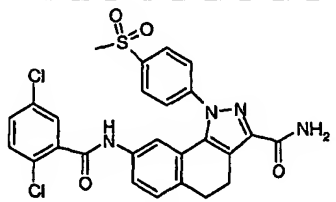
methanol and chromatographed over silica gel using ethyl acetate as eluent to give the title compound, as an oil which crystallized on standing.

Table 2.

5

Structure	Formula Weight	Name	IKK Resin IC <sub>50</sub> (μM)	Example
 HCl	418.91	8-amino-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	1 ≤ 10 μM	92
	554.55	1-[4-(methylsulfonyl)phenyl]-8-[(2-(trifluoromethyl)benzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	93
	500.58	8-[(2-methylbenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	94
	521.00	8-[(2-chlorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	95
	555.44	8-[(2,3-dichlorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	96

Structure	Formula Weight	Name	IKK Resin IC <sub>50</sub> (μM)	Example
	504.54	8-[(2-fluorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	97
	521.99	8-[(2-chloropyridin-3-yl)carbonyl]amino)-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	98
	476.52	1-[4-(methylsulfonyl)phenyl]-8-[(1H-pyrazol-4-ylcarbonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	99
	501.57	8-[(2-methylpyridin-3-yl)carbonyl]amino)-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	100
	522.53	8-[(2,3-difluorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	101
	531.55	1-[4-(methylsulfonyl)phenyl]-8-[(2-nitrobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	102

Structure	Formula Weight	Name	IKK Resin IC <sub>50</sub> (	Example
	558.61	3-[(3-(aminocarbonyl)-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazol-8-yl)amino)carbonyl]-2-methylphenyl acetate	1 ≤ 10 μM	103
	538.99	8-[(3-chloro-2-fluorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	104
	521.99	8-[(4-chloropyridin-3-carbonyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	105
	514.61	8-[(2,3-dimethylbenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	106
	516.58	8-[(3-hydroxy-2-methylbenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	107
	555.44	8-[(2,5-dichlorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	108

Structure	Formula Weight	Name	IKK Resin IC <sub>50</sub> (μM)	Example
	501.57	8-[(2-aminobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	109
	487.54	8-(isonicotinoylamino)-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	110
	566.00	8-[(2-chloro-5-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	111
	572.47	8-[(5-amino-2-chlorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	≤1 μM	112
	536.01	8-[(3-amino-4-chlorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	113
	536.01	8-[(4-amino-2-chlorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	114
	536.01	8-[(2-amino-5-chlorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	115

Structure	Formula Weight	Name	IKK Resin IC <sub>50</sub> (	Example
	536.01	8-[(3-amino-2-chlorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	116
	536.01	8-[(2-amino-4-chlorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	117
	536.01	8-[(2-amino-3-chlorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	118
	657.58	8-[(2-chloro-5-[(N,N-dimethylglycyl)amino]benzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	≤1 μM	119
	564.07	8-[[2-chloro-5-(dimethylamino)benzoyl]amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	120
	572.56	8-[(5-azido-2-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	121

Structure	Formula Weight	Name	IKK Resin IC <sub>50</sub> (μM)	Example
	527.57	8-[(4-azidobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	122
	556.43	8-[(2,5-dichloropyridin-3-yl)carbonyl]amino-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	123
	583.09	8-[(2-chloro-5-(methylsulfinyl)benzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	124
	565.01	8-[(6-chloro-1,3-benzodioxol-5-yl)carbonyl]amino-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	125
	619.13	8-[(2-chloro-5-(4-methylpiperazin-1-yl)benzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	<1 μM	126

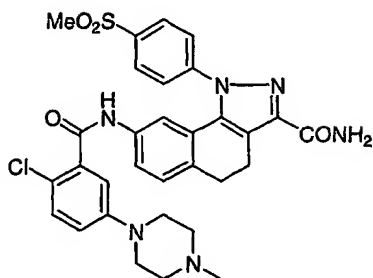
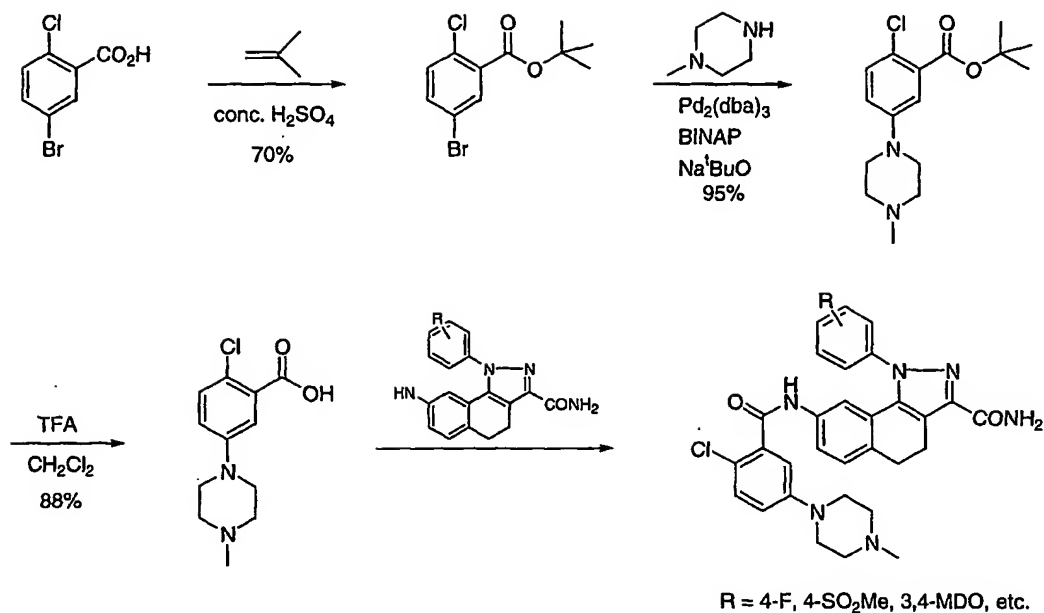
**[0069] Example 126**

8-[(2-chloro-5-(4-methylpiperazin-1-yl)benzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

5

Example 126 was synthesized using the following scheme.

Scheme XVI

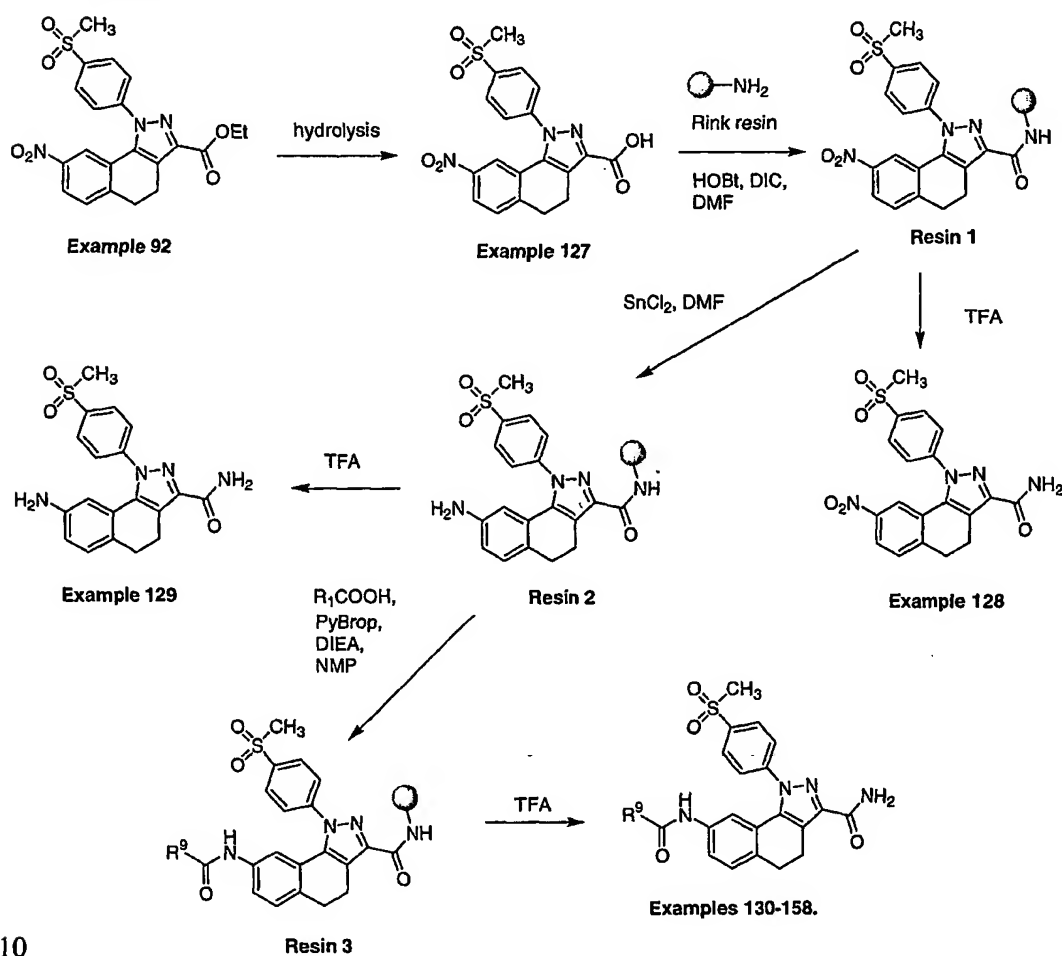


- 5 To a mixture of 2-chloro-5-(4-methylpiperazin-1-yl)benzoic acid (0.9 g, 0.0035 mol), the title compound of Example 92 (0.0024 mol) and 1 mL of diisopropylethylamine in 25 mL of DMF was added HATU (1.3 g, 0.0035 mol) in one portion. The reaction mixture was stirred at room temperature for 16 h. Solvent was removed and the residue was purified on preparative HPLC to give the product as a pale white solid (89% yield); mp: 194-195°C; <sup>1</sup>HNMR (DMSO + TFA-d, 400 MHz) δ: 10.29 (s, 1H), 8.10 (d, J = 8.7 Hz, 2H), 7.86 (d, J = 8.7 Hz, 2H), 7.64 (s, 1H), 7.43 (dd, J = 2.1, 8.2 Hz, 1H), 7.41 (s, 1H), 7.37 (dd, J = 2.0, 8.2 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.08 (dd, J = 3.0, 8.9 Hz, 1H), 7.04 (d, J = 3.0 Hz, 1H), 3.89 (d, J = 12.8 Hz, 2H), 3.51 (d, J = 12.8 Hz, 2H), 3.23 (s, 3H), 3.11 (m, 2H),
- 10

2.95 (m, 4H), 2.86 (m, 2H). The bioactivity in the IKK 2 Resin assay for the compound of Example 126 is shown in Table 2.

[0070] Examples 127-158 shown in Table 3 were synthesized by the following synthesis scheme were  $R^9$  is the appropriate aryl, substituted aryl, heteroaryl, substituted heteroaryl, substituted arylalkyl, substituted heteroarylalkyl, or cycloalkyl.

Scheme XVII



[0071] Example 127

1-[4-(methylsulfonyl)phenyl]-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxylic acid



To 5.0 g (11.3 mmol) of Example 92 (ethyl 1-[4-(methylsulfonyl)phenyl]-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxylate) in 115 mL of THF was added 115 mL of 1N NaOH and the mixture allowed to stir overnight at RT. The solution was acidified with 2N HCl and extracted three times with ethyl acetate. Combined  
5 extracts were washed with 10% aq. HCl, brine, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford 4.97 g (100%) of a yellow solid: <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) 3.00 (m, 2H), 3.11 (m, 2H), 3.31 (s, 3H), 7.39 (d, 1H), 7.67 (d, 1H), 7.90 (d, 2H), 8.07 (dd, 1H), 8.16 (d, 1H); MS (ESI+) 414 (M+1).

10 [0072] Example 128

Resin 1 and 1-[4-(methylsulfonyl)phenyl]-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

Commercially available Rink amide resin (10 g, NovaBiochem #01-64-0013, 100-  
15 200 mesh, 0.61 mmol/g) was washed sequentially with dichloromethane (DCM) and dimethylformamide (DMF). The resin was filtered, treated twice with 50% piperidine in DMF for 15 min, and subsequently washed three times each with DMF, DCM, and anhydrous DMF. To the resin was added 4.65 g of Example 127, 1.52 g of HOBt and 1.75 mL of DIC in 35 mL anhydrous DMF. After 3 h at RT,  
20 the reagents were removed by filtration and the resin washed three times each with DMF, methanol, and DCM. The resin was used directly in the next step. A small portion (approx. 100 mgs) of resin was cleaved by treatment with 20% TFA in CH<sub>2</sub>Cl<sub>2</sub> for 30 min. The resin washed twice with CH<sub>2</sub>Cl<sub>2</sub> and the collected filtrates concentrated in vacuo. The product was purified by silica chromatography to give  
25 the title compound as a light yellow solid: <sup>1</sup>H NMR(CDCl<sub>3</sub>) 9.03 (s, 2H), 8.20(d, J=8.4Hz, 2H), 8.10(dd, J=2Hz, 8.4Hz, 1H), 7.79(d, J=8.4Hz, 2H), 7.53(d, J=8.4Hz, 1H), 7.51(d, J=2Hz, 1H), 3.25(s, 3H), 3.16(m, 4H); MS(ESI+) 413 (M+1, 100).

30 [0073] Example 129

Resin 2 and 8-amino-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide, trifluoroacetic acid salt

To resin 2 (6.0 mmol) was added 50 mL of 2M SnCl<sub>2</sub>·2H<sub>2</sub>O in wet DMF. After agitation of the mixture overnight, the reagents were removed by filtration and the resin washed three times each with DMF, THF, and DCM. The resin was filtered and dried to give 10.96 g of resin 2. A 92.1 mg portion of the resin was treated twice with 20% TFA in CH<sub>2</sub>Cl<sub>2</sub> and washed three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrates were concentrated in vacuo and resin loading determined by direct cleavage NMR of the title compound: resin loading of 0.46 meq/g; <sup>1</sup>H NMR (CDCl<sub>3</sub>/TFA) 3.14 (brs, 4H), 3.31 (s, 3H), 6.78 (d, 1H, 2.0 Hz), 7.33 (dd, 1H), 7.54 (d, 1H, 8.0 Hz), 7.83 (d, 2H), 8.16 (d, 2H); MS(ESI+) 383 (M+1, 100).

**[0074] Resin 3**

Resin 2 (0.45 mmol/g, 0.200g, 90 μmol) was washed three times with anhydrous NMP and subsequently treated with 0.45 mmol of carboxylic acid R<sup>9</sup>COOH in 0.5 mL of anhydrous NMP, 0.45 mmol of PyBrop in 0.5 mL of anhydrous NMP and 0.9 mmol of DIEA. The resin was shaken at RT under N<sub>2</sub> for 2h. Subsequently, the reagents were removed by filtration, the resins retreated with the appropriate carboxylic acid, PyBrop, and DIEA in the same manner as described above. After agitation of the reaction vessels overnight at RT, the reagents were removed by filtration and the resins washed three times each with NMP, DMF, methanol, and DCM. The products were cleaved from the resins by adding 0.5 mL of 20% TFA/DCM and agitating the mixture for 15 min. The filtrate was collected and the resin retreated with additional TFA/DCM for 15 min. The resin was washed twice with DCM and the filtrates combined and concentrated in vacuo to afford the final products.

**[0075] Example 130**

8-[(cyclobutylcarbonyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

Using the method described from resin 3, the product was obtained in 57% yield as a light yellow solid: <sup>1</sup>H NMR(CDCl<sub>3</sub>/CD<sub>3</sub>OD). 8.13 (d, J=8.4 Hz, 2H), 7.76(d,

J=8.4 Hz, 2H), 7.38(d, J=1.6 Hz, 1H), 7.24(d, J=8 Hz, 1H), 6.97(dd, J=2 Hz, 8 Hz, 1H), 6.88 (s, 1H), 3.23(s, 3H), 3.10(m, 2H), 3.02(m, 1H), 2.95(m, 2H), 2.16(m, 4H), 1.95(m, 1H), 1.82(m, 1H). <sup>13</sup>C NMR(CDCl<sub>3</sub>/CD<sub>3</sub>OD): 165.0, 144.2, 142.9, 140.4, 137.1, 133.0, 129.3, 129.2, 126.4, 126.0, 123.3, 119.4, 114.8, 114.7, 60.7, 44.8, 40.6, 31.7, 29.6, 25.3, 22.8, 20.1, 18.1, 14.3. High resolution Mass: M+H<sup>+</sup> = 465.1591 (observed), 465.1608 (theoretical).

[0076] Example 131

8-[(2-chloro-4,5-dimethoxybenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

Using the method described from resin 3, the product was obtained in 62% yield as a light yellow solid: <sup>1</sup>H NMR(CDCl<sub>3</sub>). 8.14(d, J=8.8Hz, 2H), 8.03(s, 1H), 7.79(d, J=8.8Hz, 2H), 7.40(d, 1H), 7.29(m, 1H), 7.21(s, 1H), 7.16(m, 1H), 6.81(s, 1H), 3.89(s, 3H), 3.88(s, 3H), 3.14(m, 2H), 3.13(s, 3H), 2.99(m, 2H). <sup>13</sup>C NMR(CDCl<sub>3</sub>): 171.4, 164.4, 163.7, 151.7, 148.4, 144.3, 143.1, 140.8, 140.2, 136.4, 134.0, 129.6, 129.4, 126.7, 126.4, 126.1, 123.3, 122.4, 119.7, 115.3, 113.2, 113.0, 60.6, 45.0, 29.8, 21.3, 20.2. High resolution Mass: M+H<sup>+</sup> = 581.1277 (observed), 581.1256(theoretical).

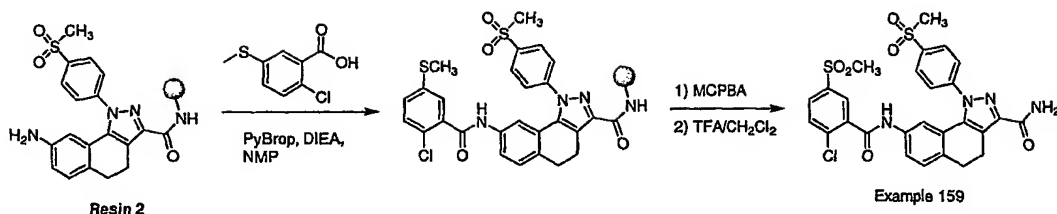
[0077] Examples 132-158

The compounds of Examples 132-158 were prepared as previously described for Example 130 using the appropriate aryl, substituted aryl, heteroaryl, substituted heteroaryl, substituted arylalkyl, substituted heteroarylalkyl, or cycloalkyl and are listed in Table 3.

[0078] Example 159

8-[[2-chloro-5-(methylsulfonyl)benzoyl]amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

Scheme XVIII

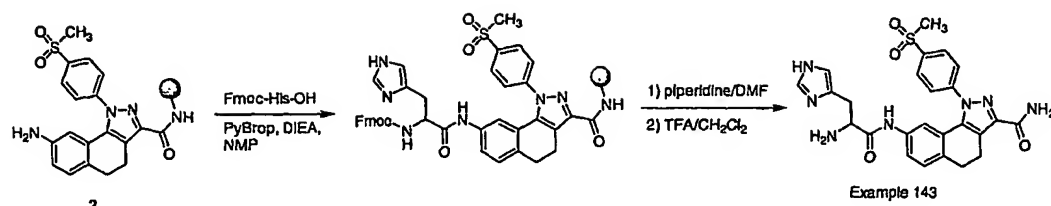


To 0.30 g of amino resin 2 (pretreated in DCM for two hrs and washed with dry NMP) was added PyBrop (0.42g, 0.90 mmol), 2-chloro-5-methylthiobenzoic acid (182mg, 0.9 mmol), DIEA(314 uL, 1.8 mmol) and dry NMP (2 mL). The resin was shaken for two hrs. The excess reagents were drained, and the resin was washed with DMF(x3), methanol (x3), and DCM (x3), and treated with 20% TFA/DCM mixture containing 1% triisopropylsilane (2 x 12 min x 3 mL). The resin was washed with DMC (2 x 4 mL). The combined filtrate and washings were evaporated to a solid, which was further dissolved in 10 mL of DCM. To the resulting solution was added MCPBA (440 mg, 77% pure, 1.96 mmol ). After 3h, the reaction was quenched with 30 mL ethylacetate. The organic phase was washed with sat. sodium bicarbonate (x3) and brine (x2), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica chromatography with 8:2 EtOAc/hexane. The product was isolated as light yellow solid, 37 mg (34%):  $^1\text{H}$  NMR( $\text{CDCl}_3/\text{CD}_3\text{OD}$ ) 8.00(d,  $J=8.8\text{Hz}$ , 2H), 7.83(s, 1H), 7.81(dd, 1H), 7.68(d,  $J=8.4\text{Hz}$ , 2H), 7.51(d,  $J=8.4\text{Hz}$ , 1H), 7.34(s, 1H), 7.25-7.17(m, 2H), 3.02(s, 3H), 2.98(s, 3H), 2.96(m, 2H), 2.88(m, 2H). LC-MS: 599.0 ( $\text{M}+\text{H}^+$ ). High resolution Mass:  $\text{M}+\text{NH}_4^+=616.1077$  (observed), 616.1086(theoretical).

[0079] Example 160

8-(L-histidylamino)-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

SCHEME XIX

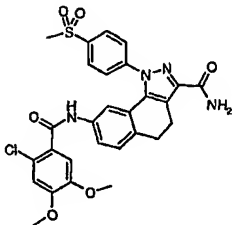
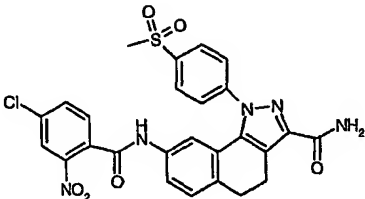
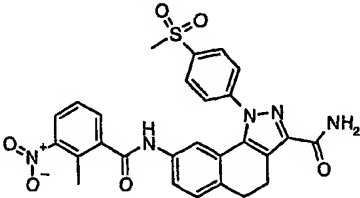
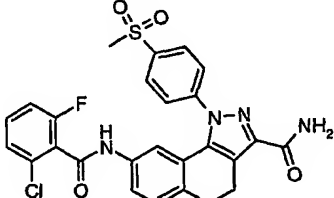
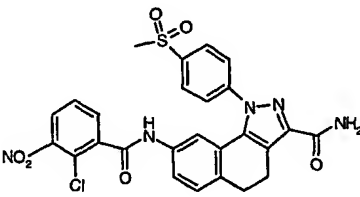
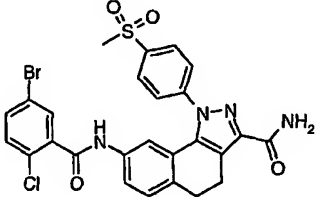


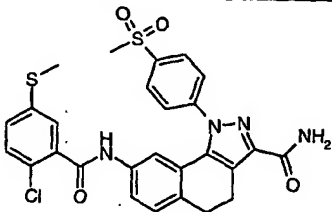
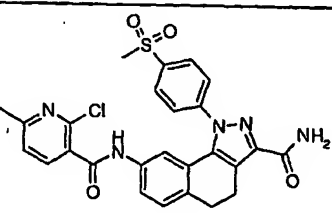
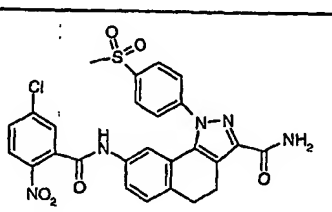
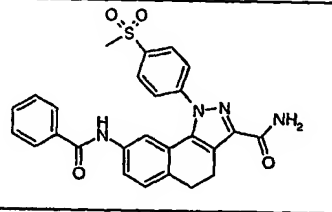
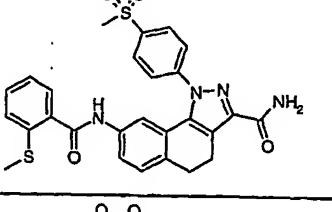
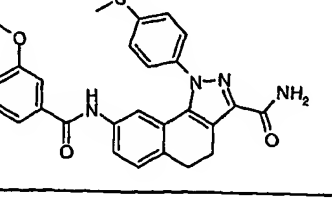
Amino resin 3 (0.402 mmols/g, 0.0804 mmols, 0.200g) was pre-treated in DCM for one hour followed by washing using anhydrous NMP. To this resin added 5.0 equiv. of Fmoc-His-OH (0.402 mmols, 152 mg) followed by addition of PyBrop (NovaBiochem, 0.402 mmols, 187 mg). To this mixture was added 10.0 equiv. of DIEA (0.804 mmols, 140  $\mu$ l) followed by addition of anhydrous NMP (1 ml). Reaction vessel was capped and agitated under nitrogen for two hours. Reagents were removed by filtration and the resin washed as follows: NMP (x3), DMF (x3), DCM (x3), and anhydrous NMP (x1). Retreated resin as described above and let agitate under nitrogen overnight. Drained vessel and washed as follows: NMP (x3), DMF (x3), MeOH (x3), DCM (x3), and DMF (x1). Deprotected Fmoc group using 50:50 piperidine/DMF (x2, 2ml) 40 minutes each. Washed resin as follows: DMF (x3), MeOH (x3), and DCM (x3). Let resin air dry for approximately one hour. Resin was then treated with 20:80 TFA/DCM containing 1% triisopropylsilane (x2, 1 ml, 45 minutes). Collected filtrates and washed resin with DCM (x3, 1ml). Collected all washings and remove volatiles under nitrogen to afford 17.2 mg of an orange solid.  $MS^+ + 1$  ( $C_{25}H_{25}N_7O_4S$ ): 520 (measured).

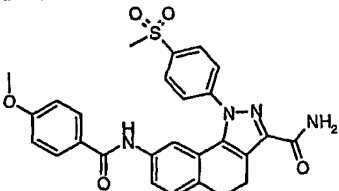
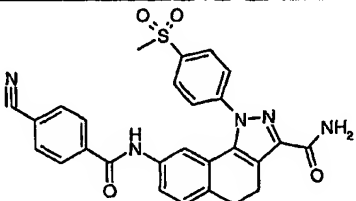
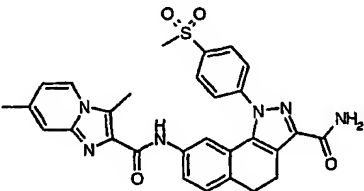
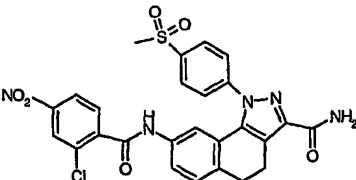
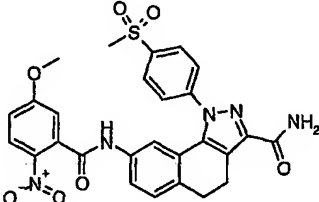
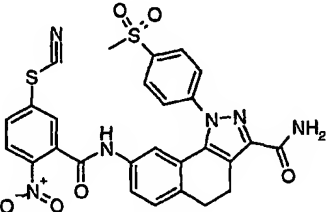
20

Table 3.

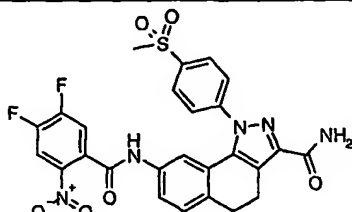
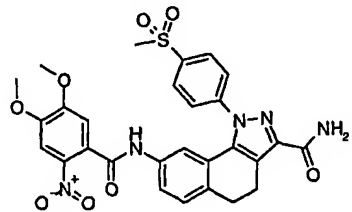
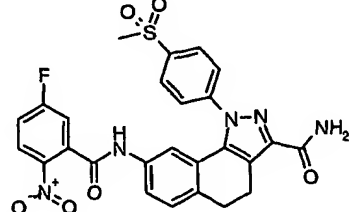
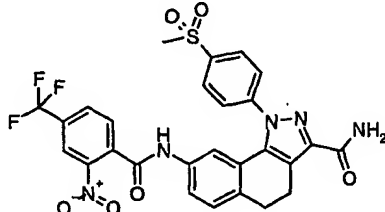
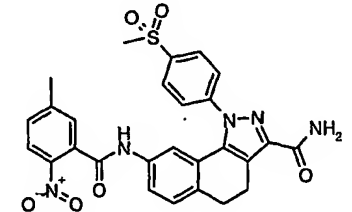
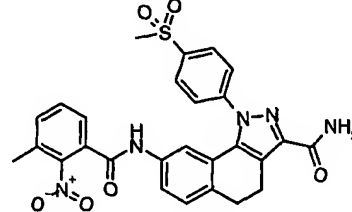
Structure	Formula Weight	Name	IKK Resin $IC_{50}$	Example
	464.55	8-[[[(cyclobutylcarbonyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10$ $\mu$ M	130

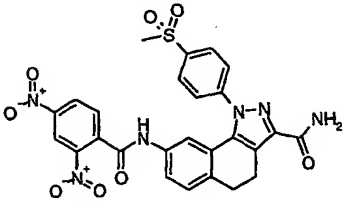
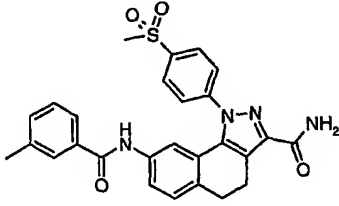
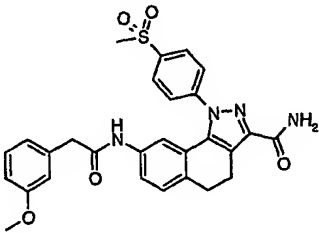
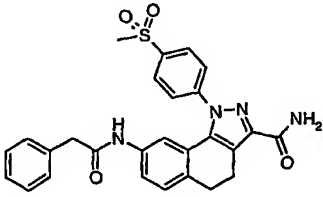
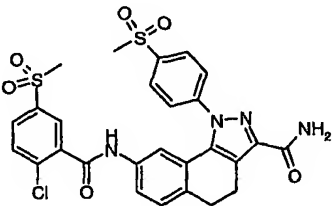
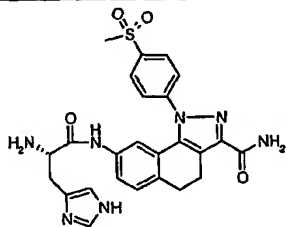
Structure	Formula Weight	Name	IKK Resin IC <sub>50</sub>	Example
	581.05	8-[(2-chloro-4,5-dimethoxybenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	131
	566.00	8-[(4-chloro-2-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	132
	545.58	8-[(2-methyl-3-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	133
	538.99	8-[(2-chloro-6-fluorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	134
	566.00	8-[(2-chloro-3-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	135
	599.89	8-[(5-bromo-2-chlorobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	136

Structure	Formula Weight	Name	IKK Resin IC <sub>50</sub>	Example
	567.09	8-([2-chloro-5-(methylthio)benzoyl]amino)-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	137
	536.01	8-([(2-chloro-6-methylpyridin-3-yl)carbonyl]amino)-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	138
	566.00	8-[(5-chloro-2-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	139
	486.55	8-(benzoylamino)-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	140
	532.64	1-[4-(methylsulfonyl)phenyl]-8-([2-(methylthio)benzoyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	142
	516.58	8-[(3-methoxybenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	142

Structure	Formula Weight	Name	IKK Resin IC <sub>50</sub>	Example
	516.58	8-[(4-methoxybenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	143
	511.56	8-[(4-cyanobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	144
	554.63	8-[(3,7-dimethylimidazo[1,2-a]pyridin-2-yl)carbonylamino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	145
	566.00	8-[(2-chloro-4-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	146
	561.58	8-[(5-methoxy-2-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	147
	588.63	3-[(3-(aminocarbonyl)-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazol-8-yl)amino]carbonyl-4-nitrophenyl thiocyanate	≤1 μM	148



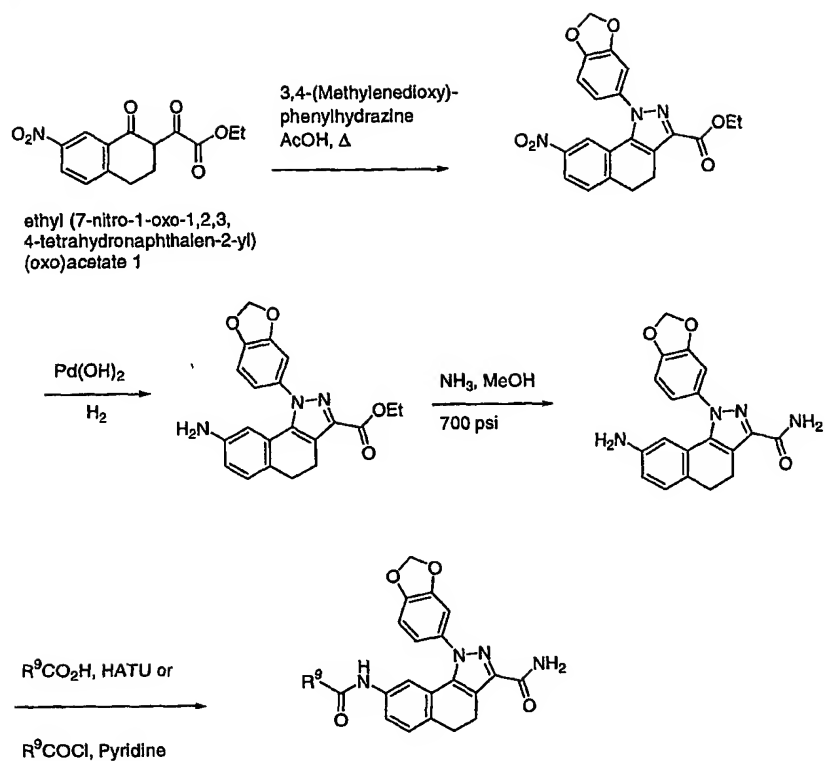
Structure	Formula Weight	Name	IKK Resin IC <sub>50</sub>	Example
	567.53	8-[(4,5-difluoro-2-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	149
	591.60	8-[(4,5-dimethoxy-2-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	150
	549.54	8-[(5-fluoro-2-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	151
	599.55	1-[4-(methylsulfonyl)phenyl]-8-[(2-nitro-4-(trifluoromethyl)benzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	152
	545.58	8-[(5-methyl-2-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	153
	545.58	8-[(3-methyl-2-nitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	154

Structure	Formula Weight	Name	IKK Resin IC <sub>50</sub>	Example
	576.55	8-[(2,4-dinitrobenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	155
	500.58	8-[(3-methylbenzoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	156
	530.61	8-[(3-methoxyphenyl)acetyl]amino-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	157
	500.58	1-[4-(methylsulfonyl)phenyl]-8-[(phenylacetyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	158
	599.09	8-[[2-chloro-5-(methylsulfonyl)benzoyl]amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	159
	519.59	8-(L-histidylamino)-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	160

[0080] Examples 161-206

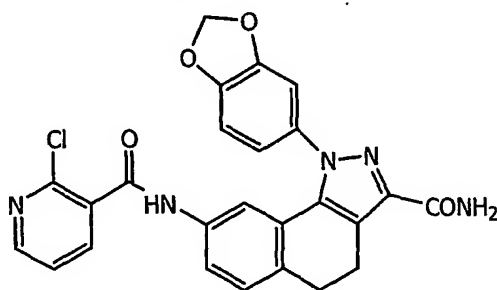
Examples 161-206 shown in Table 4 were synthesized using the following synthesis procedure similar to Scheme I where R<sup>9</sup> is the appropriate aryl, substituted aryl, heteroaryl, substituted heteroaryl, substituted arylalkyl, substituted heteroarylalkyl, or cycloalkyl. The detailed synthesis of 1-(1,3-benzodioxol-5-yl)-8- $\{[(2$ -  
5 chloropyridin-3-yl)carbonyl]amino}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (Example 161) is described below and is illustrative for the compounds of Table 4.

## SCHEME XX

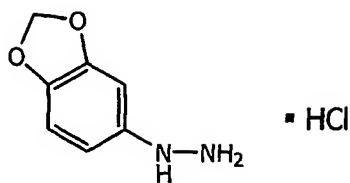


## 5 [0081] Example 161

1-(1,3-benzodioxol-5-yl)-8-[[[(2-chloropyridin-3-yl)carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

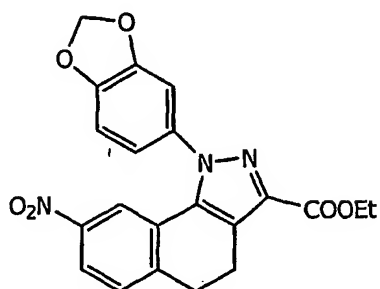


## 10 [0082] Step 1



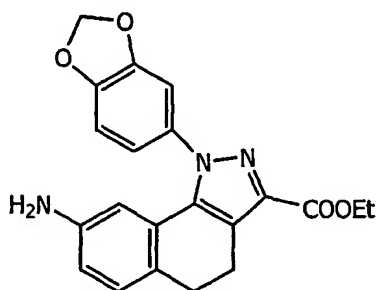
The title compound of step 1 was prepared by the method disclosed by T. Komatsu et al, *Azneim.-Forsch.* (1972) 22(12), 2099-104.

5 [0083] Step 2



A mixture of 5.00g (17.2 mmoles) of diketo ester and 3.24g (17.2 mmoles) of the title product of Step 1 in 100ml of acetic acid was refluxed with stirring for 3h, and then cooled. The mixture was concentrated, and the residue triturated with ethyl acetate affording a brown solid which was filtered, washed with ethyl acetate, and dried to give the title compound, 4.79g. The structure was supported by  $^1\text{H}$  NMR.

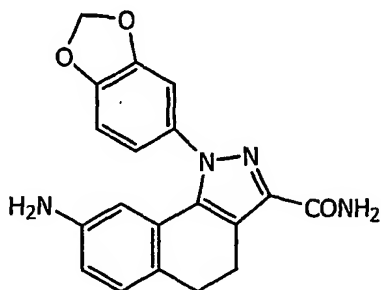
[0084] Step 3



15 A solution 4.79g of the title product of Step 2 in acetic acid was treated at room temperature with 5% palladium on carbon under an atmosphere of hydrogen gas at 5 psi. The reaction was followed by LC-MS. When the conversion was complete, the mixture was filtered and concentrated to give the title compound as a brownish oil that was used directly for the next step.

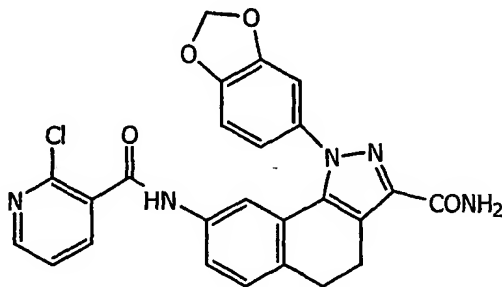
**[0085] Step 4**

8-amino-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



5

The title product of Step 3 was dissolved in anhydrous ethanol and then an approximately equal volume of liquid ammonia was added. The resulting mixture was sealed in a pressure vessel and then stirred overnight at 100°C. After cooling, the mixture was concentrated. The residue was taken up in dichloromethane – methanol and chromatographed over silica gel using ethyl acetate as eluent to give the title compound, 890mg, as an oil which crystallized on standing. Anal. for C<sub>19</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>·0.75 H<sub>2</sub>O (MW 361.87): Calc'd.: C, 63.06%, H, 4.46%, N, 15.48%. Found: C, 63.24%; H, 4.70%; N, 14.58%.

15 **[0086] Step 5**

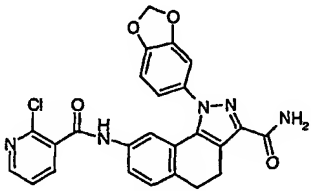
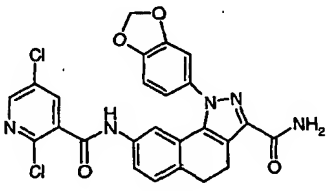
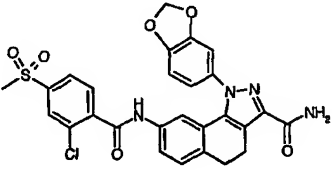
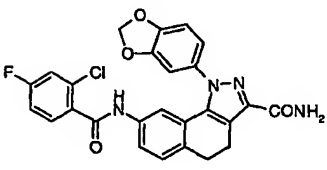
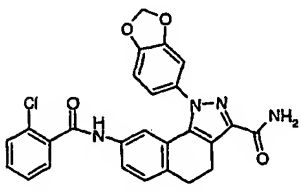
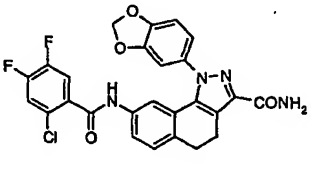
A mixture of the title product of Example 4 (3.6 g, 0.01 mol) and 2-chloronicotinyl chloride (1.8 g, 0.01 mol) in 50 ml of pyridine was stirred at room temperature overnight. Solvent was removed and the residue was triturated with a mixture of acetonitrile and methanol (20:1) to give 2.6 g of the title compound as a light brown solid. The mother liquor was concentrated and purified the same way to give

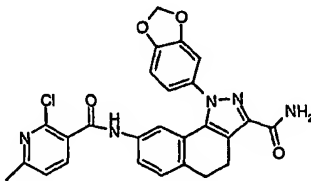
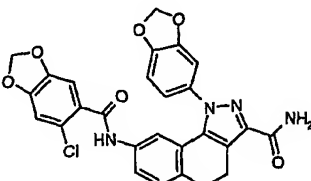
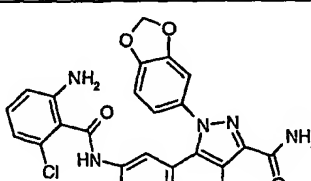
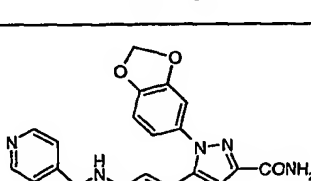
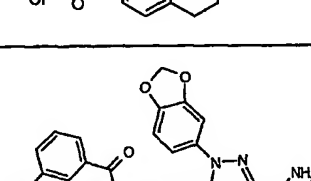
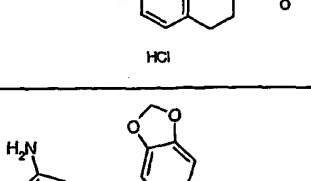
20

another 0.69 g of product (68% yield); mp: 165-166C. Anal. Calcd. for  $C_{25}H_{18}ClN_5O_4 \cdot 0.5 H_2O$ : C, 60.43; H, 3.85; 14.09. Found: C, 60.27; H, 3.59; N, 14.14.

5

Table 4

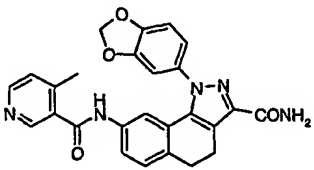
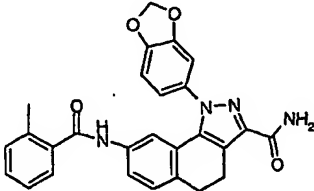
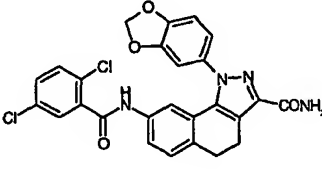
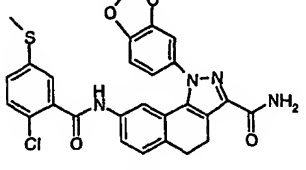
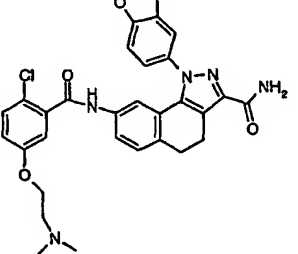
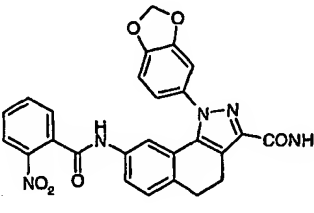
Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	Example
	487.90	1-(1,3-benzodioxol-5-yl)-8-([(2-chloropyridin-3-yl)carbonyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu M$	161
	522.35	1-(1,3-benzodioxol-5-yl)-8-([(2,5-dichloropyridin-3-yl)carbonyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu M$	162
	565.01	1-(1,3-benzodioxol-5-yl)-8-([2-chloro-4-(methylsulfonyl)benzoyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu M$	163
	504.91	1-(1,3-benzodioxol-5-yl)-8-[(2-chloro-4-fluorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu M$	164
	486.92	1-(1,3-benzodioxol-5-yl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu M$	165
	522.90	1-(1,3-benzodioxol-5-yl)-8-[(2-chloro-4,5-difluorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu M$	166

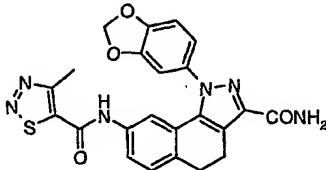
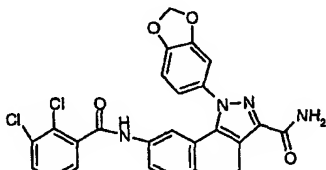
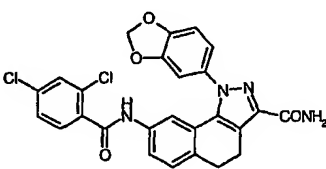
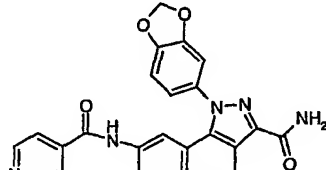
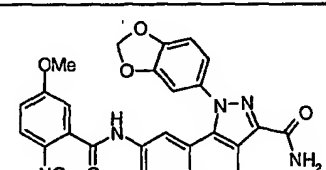
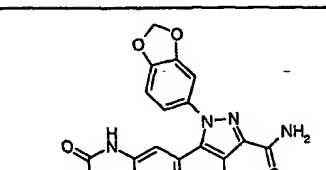
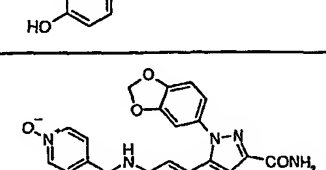
Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	Example
	501.93	1-((2-chloro-6-methylpyridin-3-yl)carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	167
	530.93	1-((6-chloro-1,3-benzodioxol-5-yl)carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	168
	501.93	8-((2-amino-6-chlorobenzoyl)amino)-1-((1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	169
	487.91	1-((3-chloroisonicotinoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	170
	538.39	8-((3-amino-2-chlorobenzoyl)amino)-1-((1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$\leq 1 \mu\text{M}$	171
	501.93	8-((5-amino-2-chlorobenzoyl)amino)-1-((1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	172

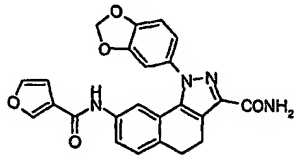
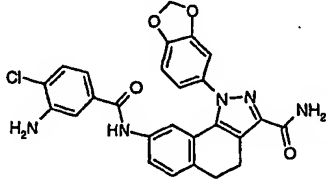
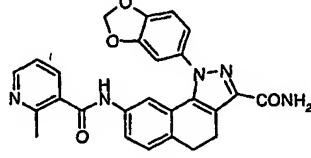
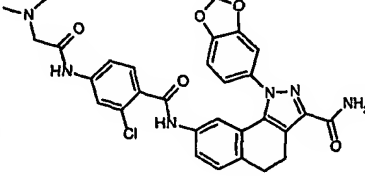
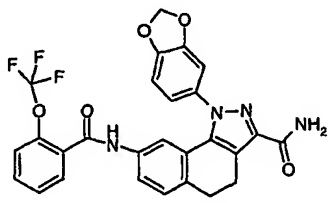
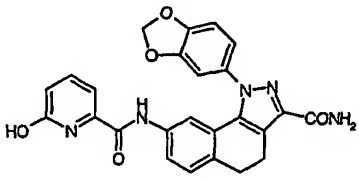
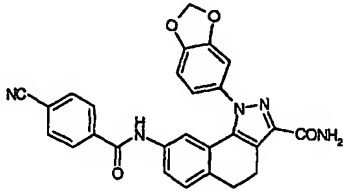


Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	Example
	531.92	1-((2-chloro-5-nitrobenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	173
	546.97	1-((2-chloro-4,5-dimethoxybenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	174
	546.97	1-((2-chloro-3,4-dimethoxybenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	175
	549.01	1-((2-chloro-5-(methylsulfinyl)benzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	176
	531.37	1-((2-bromobenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	177
	516.95	1-((2-chloro-5-methoxybenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	178
	494.51	8-((4-acetylbenzoyl)amino)-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	179

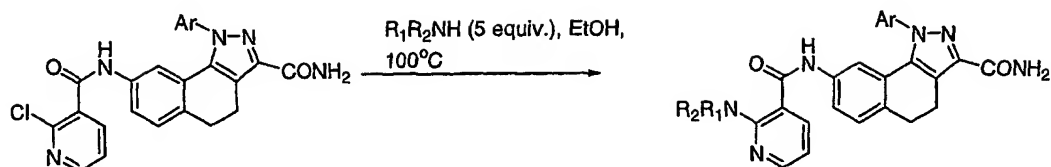
Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	Example
	501.93	8-[(4-amino-2-chlorobenzoyl)amino]-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	180
	555.90	1-(1,3-benzodioxol-5-yl)-8-([2-chloro-6-(trifluoromethyl)pyridin-3-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	181
	516.95	1-(1,3-benzodioxol-5-yl)-8-[(2-chloro-4-methoxybenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	182
	529.99	1-(1,3-benzodioxol-5-yl)-8-([2-chloro-5-(dimethylamino)benzoyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	183
	531.92	1-(1,3-benzodioxol-5-yl)-8-[(2-chloro-4-nitrobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	184
	565.01	1-(1,3-benzodioxol-5-yl)-8-([2-chloro-5-(methylsulfonyl)benzoyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	185
	469.46	1-(1,3-benzodioxol-5-yl)-8-([(6-hydroxypyridin-3-yl)carbonyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	186

Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	Example
	467.49	1-((1,3-benzodioxol-5-yl)-8-((4-methylpyridin-3-yl)carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	187
	466.50	1-((1,3-benzodioxol-5-yl)-8-((2-methylbenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	188
	521.36	1-((1,3-benzodioxol-5-yl)-8-((2,5-dichlorobenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	189
	533.01	1-((1,3-benzodioxol-5-yl)-8-((2-chloro-5-(methylthio)benzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	190
	574.04	1-((1,3-benzodioxol-5-yl)-8-((2-chloro-5-(2-(dimethylamino)ethoxy)benzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	191
	497.47	1-((1,3-benzodioxol-5-yl)-8-((2-nitrobenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	192

Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	Example
	474.50	1-((1,3-benzodioxol-5-yl)-8-((4-methyl-1,2,3-thiadiazol-5-yl)carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	193
	521.36	1-((1,3-benzodioxol-5-yl)-8-((2,3-dichlorobenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	194
	521.36	1-((1,3-benzodioxol-5-yl)-8-((2,4-dichlorobenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	195
	453.46	1-((1,3-benzodioxol-5-yl)-8-(isonicotinoylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	196
	527.50	1-((1,3-benzodioxol-5-yl)-8-((5-methoxy-2-nitrobenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	197
	482.50	1-((1,3-benzodioxol-5-yl)-8-((3-hydroxy-2-methylbenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	198
	469.46	1-((1,3-benzodioxol-5-yl)-8-((1-oxidoisonicotinoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	199

Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	Example
	442.44	1-(1,3-benzodioxol-5-yl)-8-(3-furoylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	200
	501.93	8-[(3-amino-4-chlorobenzoyl)amino]-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	201
	467.49	1-(1,3-benzodioxol-5-yl)-8-[(2-methylpyridin-3-yl)carbonyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	202
	587.04	1-(1,3-benzodioxol-5-yl)-8-[(2-chloro-4-[(N,N-dimethylglycyl)amino]benzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	203
	536.46	1-(1,3-benzodioxol-5-yl)-8-[[2-(trifluoromethoxy)benzoyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	204
	469.46	1-(1,3-benzodioxol-5-yl)-8-[(6-hydroxypyridin-2-yl)carbonyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	205
	477.48	1-(1,3-benzodioxol-5-yl)-8-[(4-cyanobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	206

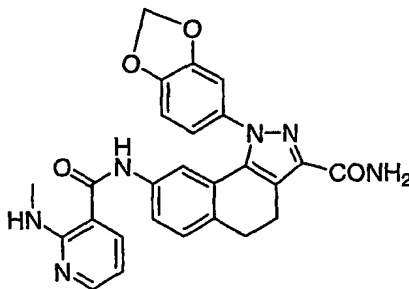
## [0087] SCHEME XXI



5

## [0088] Example 207

1-(1,3-benzodioxol-5-yl)-8-({[2-(methylamino)pyridin-3-yl]carbonyl}amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



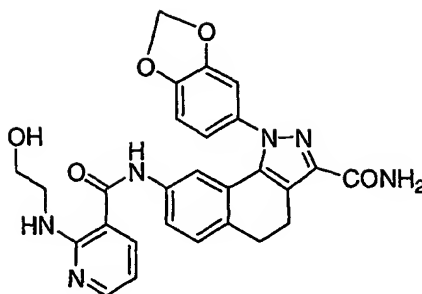
10

A mixture of the title product of Example 161 (1.4 g, 0.0028 mol) and methylamine (0.014 mol) in 6 mL EtOH was heated in a sealed tube to 100°C for 48 h. The off-white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH and Et<sub>2</sub>O to afford 1.05 g of title compound (yield: 75%). Mp: 273-275°C. <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): δ 2.88-2.95 (m, 4H + 3H), 6.12 (s, 2H), 6.57-6.61 (dd, 1H, *J* = 7.6 Hz, 4.7 Hz), 6.95-6.98 (dd, 1H, *J* = 8 Hz, 2 Hz), 7.07 (d, 1H, *J* = 8 Hz), 7.13 (d, 1H, *J* = 2 Hz), 7.25-7.34 (m, 3H), 7.45-7.50 (m, 2H), 7.82-7.83 (m, 1H), 7.91-7.95 (dd, 1H, *J* = 7.6 Hz, 1.7 Hz), 8.18-8.20 (dd, 1H, *J* = 4.8 Hz, 1.8 Hz), 10.02 (s, 1H). *M* + 1 = 483.

20

## [0089] Example 208

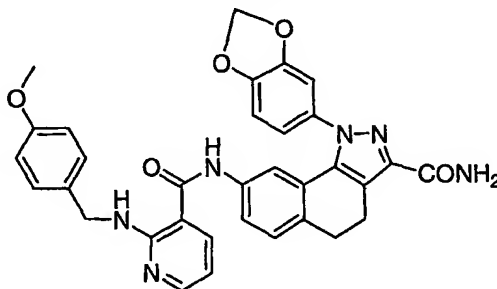
1-(1,3-benzodioxol-5-yl)-8-({[2-[(2-hydroxyethyl)amino]pyridin-3-yl]carbonyl}amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



The title compound was synthesized by the same procedure as in Example 207 starting with product of Example 161 (1g, 0.0020 mol) and ethanolamine (0.626g, 0.010 mol) in 4 mL of EtOH to afford 0.475 g of title compound (yield: 46 %). Mp: 250-253 °C. <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): δ 2.86-2.93 (m, 4H), 3.43-3.47 (m, 2H), 3.53-3.54 (m, 2H), 4.76 (s, 1H), 6.12 (s, 2H), 6.56-6.59 (dd, 1H, *J* = 7.5 Hz, 4.8 Hz), 6.95-6.97 (dd, 1H, *J* = 8 Hz, 2 Hz), 7.05 (d, 1H, *J* = 8 Hz), 7.11 (d, 1H, *J* = 2 Hz), 7.26-7.37 (m, 4H), 7.51 (s, 1H), 7.89-7.91 (dd, 1H, *J* = 7.6 Hz, 1.5 Hz), 7.97-7.99 (t, 1H, *J* = 5 Hz), 8.14-8.15 (dd, 1H, *J* = 4.7 Hz, 1.6 Hz), 10.02 (s, 1H). Anal. Calcd. for C<sub>27</sub>H<sub>24</sub>N<sub>6</sub>O<sub>5</sub>: C, 63.27; H, 4.72; N, 16.40. Found: C, 63.38; H, 4.7; N, 16.34. *M* + 1 = 513.

#### [0090] Example 209

1-(1,3-benzodioxol-5-yl)-8-[(2-[(4-methoxybenzyl)amino]pyridin-3-yl)carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



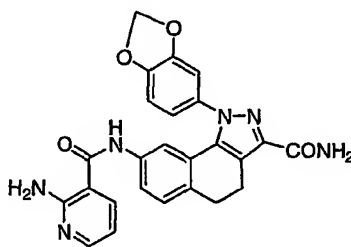
The title compound was synthesized by the same procedure as in Example 207 starting with product of Example 161 (2 g, 0.0040 mol) and *p*-methoxybenzylamine (2.8 g, 0.020 mol) in 10 mL EtOH to yield 1.96 g of the title compound (yield: 60%). Mp: 181-182°C. <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): δ 2.88-2.94 (m, 4H), 3.71 (s, 3H), 4.56 (d, 2 H, *J* = 5.6 Hz), 5.98 (s, 2H), 6.60-6.64 (dd, 1H, *J* = 7.5 Hz, 4.7 Hz), 6.88 (d, 2H, *J* = 8.4 Hz), 6.96 (s, 2H), 7.11 (s, 1H), 7.23-7.35 (m, 5 H), 7.39 (s,

1H), 7.49 (s, 1H), 7.95 (d, 1H,  $J = 7.45$  Hz), 8.17 (d, 1H,  $J = 4.7$  Hz), 8.23 (t, 1H,  $J = 5.6$  Hz), 10.06 (s, 1H). Anal. Calc. for  $C_{33}H_{28}N_6O_5$ : C, 67.34; H, 4.79; N, 14.28. Found C, 67.08; H, 4.78; N, 14.19.  $M + 1 = 589$ .

5

**[0091] Example 210**

8-[[[(2-aminopyridin-3-yl)carbonyl]amino]-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

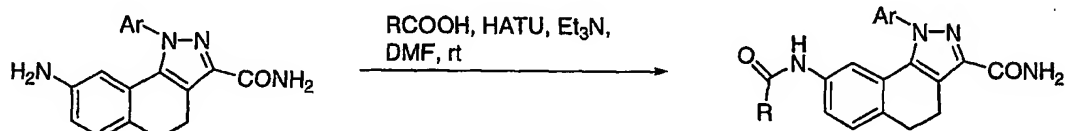


10

The title compound of Example 209 (1.96 g, 0.0033 mol) was dissolved in 6 mL  $CH_2Cl_2$  and reacted with 5 mL TFA at room temperature for 36 h. The crude reaction mixture was diluted with  $CH_2Cl_2$  and basified with a saturated aqueous solution of  $Na_2CO_3$ . The layers were separated and the organic layer was dried over  $MgSO_4$ . The residue obtained after removal of the solvent under vacuum was triturated with EtOH to afford 0.503 g of title compound (yield: 32%). Mp: 265-267 °C.  $^1H$  NMR (300 MHz,  $d_6$ -DMSO):  $\delta$  2.88-2.95 (m, 4H), 6.12 (s, 2H), 5.58-6.62 (dd, 1H,  $J = 7.6$  Hz, 4.7 Hz), 6.97-7.08 (m, 4H), 7.17 (d, 1H,  $J = 1.9$  Hz), 7.28 (s, 1H), 7.32 (s, 2H), 7.55 (s, 2H), 7.95-7.98 (dd, 1H,  $J = 7.7$  Hz, 1.7 Hz), 8.11-8.13 (dd, 1H,  $J = 4.7$  Hz, 1.7 Hz), 9.99 (s, 1H).  $M + 1 = 469$ .

20

**SCHEME XXII**

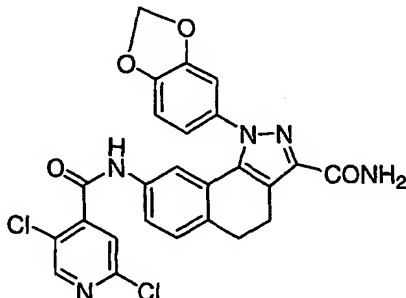


25



**[0092] Example 211**

1-(1,3-benzodioxol-5-yl)-8-[(2,5-dichloroisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



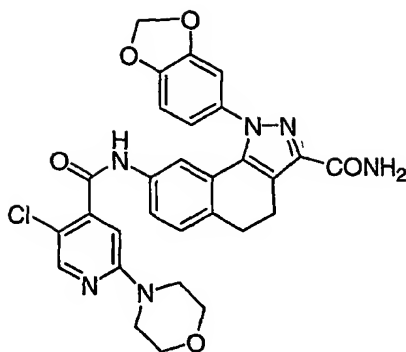
5 2,5-Dichloroisonicotinic acid (1.65g, 0.0086 mol), HATU (3.27g, 0.0086 mol) and finally Et<sub>3</sub>N (2.32 mL, 0.0166 mol) were added to a solution of the title compound of step 4 of Example 161 (2g, 0.00574 mol) in 29 mL of DMF. The reaction mixture was stirred at room temperature for 3 h. The completion of the reaction was confirmed by monitoring the disappearance of the title compound of step 4 of

10 Example 161 in LC/MS. The crude reaction mixture was concentrated to about 10 mL of DMF. Upon addition of water to this DMF residue, a white solid was formed. This white solid was triturated in water for 20 min and filtered. The solid was collected, dissolved in THF, and dried with MgSO<sub>4</sub>. Removal of the solvent afforded a brown solid that was triturated in warm CH<sub>3</sub>CN (80°C) to give 2.2g of

15 the title compound (yield 73%). Mp: 292-293°C. <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): δ 2.90-2.92 (m, 4H), 6.09 (s, 2H), 6.94-7.04 (m, 2H), 7.12 (d, 1H, *J* = 2 Hz), 7.26-7.38 (m, 4H), 7.51 (s, 1H), 7.81 (s, 1H), 8.61 (s, 1H), 10.54 (s, 1H). *M* + 1 = 523.

**[0093] Example 212**

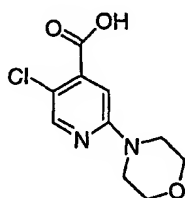
20 1-(1,3-benzodioxol-5-yl)-8-[(5-chloro-2-morpholin-4-ylisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



## [0094] Step 1

5-chloro-2-morpholin-4-ylisonicotinic acid

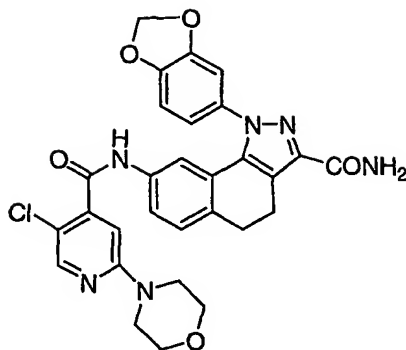
5



2,5-Dichloroisonicotinic acid, prepared by the method of E. Marzi, A. Bigi, M. Schlosser, *Eur. J. Org. Chem.* 2001, 1371 - 1376, (1.6g, 0.0083 mol) and morpholine (10.9g, 0.125 mol) in 4 mL of N,N-dimethylacetamide were heated at 80°C for 4 days. The volatiles were removed under vacuum and the resulting yellow solid partitioned between water and Et<sub>2</sub>O. The aqueous layer was acidified to pH = 1.5 using an aqueous solution of HCl and extracted once with Et<sub>2</sub>O (25 mL) and three times with CH<sub>2</sub>Cl<sub>2</sub> (25 mL). The organic extracts were combined and the solvents removed under vacuum. The resulting yellow solid was crystallized from MeOH to afford the title compound 1.07 g (yield: 34 %). <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): δ 3.45 (t, 4H, *J* = 4.8 Hz), 3.67 (t, 4H, *J* = 4.8 Hz), 7.06 (s, 1H), 8.21 (s, 1H), 13.79 (s (broad), 1H). <sup>13</sup>C HMR (100 MHz, *d*<sub>6</sub>-DMSO): δ 45.6, 66.4, 107.3, 116.1, 141.3, 148.3, 158.5, 166.8. *M* + 1 = 243.

## [0095] Step 2

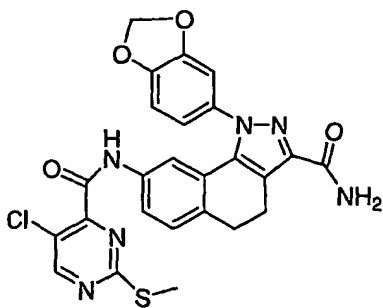
1-(1,3-benzodioxol-5-yl)-8-[(5-chloro-2-morpholin-4-ylisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



The title compound was synthesized by the same procedure as in Example 211 starting with the title material from step 1 (0.35 g, 0.00144 mol), the title compound of step 4 of Example 161 (0.333 g, 0.00096 mol), HATU (0.54 g, 0.00142 mol) and Et<sub>3</sub>N (0.39 mL, 0.00279 mol) in DMF (8 mL) to yield 0.487 g of the title compound (yield: 88%). Mp: 269-271°C. <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): δ 2.88-2.93 (m, 4H), 3.46 (t, 4H, *J* = 4.6 Hz), 3.66 (t, 4H, *J* = 4.6 Hz), 6.09 (s, 2H), 6.94 (s, 1H), 6.97 (d, 1H, *J* = 2 Hz), 7.02 (d, 1H, *J* = 8.2 Hz), 7.11 (d, 1H, *J* = 1.9 Hz), 7.25 (s, 1H), 7.29-7.32 (m, 2 H), 7.39-7.42 (dd, 1H, *J* = 8.2 Hz, 2 Hz), 7.5 (s, 1H), 8.19 (s, 1H), 10.36 (s, 1H). *M* + 1 = 574.

#### [0096] Example 213

1-(1,3-benzodioxol-5-yl)-8-({[5-chloro-2-(methylthio)pyrimidin-4-yl]carbonyl}amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

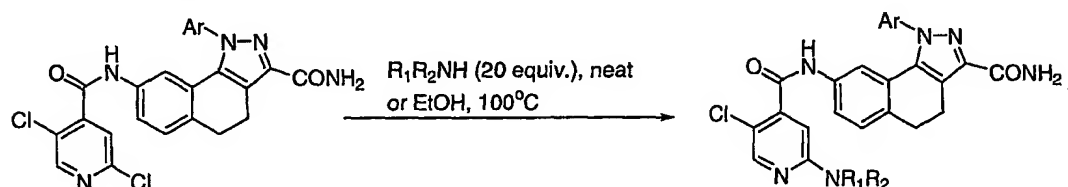


The title compound was synthesized by the same procedure as in Example 211 starting with 5-chloro-2-(methyl-thio)pyrimidine-4 carboxylic acid (1.76 g, 0.00861 mol), the title compound of step 4 of Example 161 (2 g, 0.00574 mol), HATU (3.27 g, 0.00857mol), and Et<sub>3</sub>N (2.32 mL, 0.0166 mol) in DMF (29 mL) to yield 1.3 g of

the title compound (yield: 42%).  $^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO):  $\delta$  2.52 (s, 3H), 2.88-2.93 (m, 4H), 6.08 (s, 2H), 6.94-6.97 (dd, 1H,  $J = 8.2$  Hz, 1.9 Hz), 7.01 (d, 1H,  $J = 8.2$  Hz), 7.11 (d, 1H,  $J = 1.9$  Hz), 7.25-7.33 (m, 3H), 7.38-7.41 (dd, 1H,  $J = 8.2$  Hz, 1.9 Hz), 7.5 (s, 1H), 8.88 (s, 1H), 10.59 (s, 1H).  $M + 1 = 536$ .

5

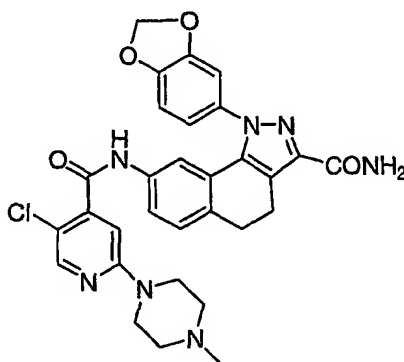
## SCHEME XXIII



10

## [0097] Example 214

1-(1,3-benzodioxol-5-yl)-8-([5-chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



15

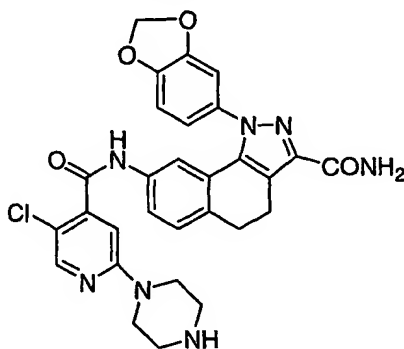
A mixture of the title compound of Example 211 (1.2g, 0.0023 mol) and N-methylpiperazine (4.6 mL, 0.046 mol) was heated at 100°C in a sealed tube for 24 h. The completion of the reaction was checked by HPLC. After removal of the volatiles under vacuum, the residue was partitioned between water and  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed an additional time with water and dried over  $\text{MgSO}_4$ . The crude product mixture was purified by chromatography on silica gel using  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 12/1 to 10/2 to give 0.62g of the title product, yield: 46%. Mp: 305-307°C.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO):  $\delta$  2.18 (s, 3H), 2.34-2.35 (d, 2H,  $J = 5$

20

Hz), 2.89-2.91 (m, 4H), 3.49 (d, 2H,  $J = 5$  Hz), 6.08 (s, 2H), 6.91-7.03 (m, 3H), 7.1 (d, 1H,  $J = 2$  Hz), 7.24-7.3 (m, 3H), 7.38-7.41 (dd, 1H,  $J = 8.3$  Hz, 2 Hz), 7.49 (s, 1H), 8.13 (s, 1H), 10.33 (s, 1H).  $M + 1 = 587$ .

5 [0098] Example 215

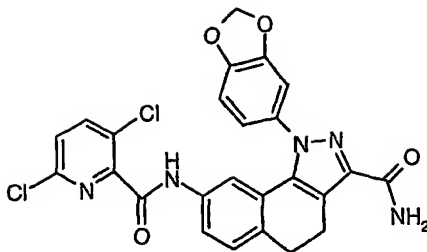
1-(1,3-benzodioxol-5-yl)-8-[(5-chloro-2-piperazin-1-ylisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



The title compound was synthesized by the same procedure as in Example 214  
 10 starting with the title compound of Example 211 (1g, 0.0018 mol) and piperazine (3  
 g, 0.036 mol) in EtOH (4 mL). The reaction was run at 95°C for 24h. After  
 allowing the reaction mixture to cool down, the volatiles were removed under  
 vacuum. The residue was triturated with H<sub>2</sub>O and finally with EtOH to yield 0.572  
 g of the title compound (yield: 55%). <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): δ 2.71 (s,  
 15 broad, 4H), 2.86-3.30 (m, 4H), 3.39 (s, broad, 4H), 6.07 (s, 2H), 6.85 (s, 1H), 6.93-  
 6.95 (dd, 1H,  $J = 8.2$  Hz, 1.9 Hz), 7.00 (d, 1H,  $J = 8.2$  Hz), 7.09 (d, 1H,  $J = 1.9$  Hz),  
 7.24-7.30 (m, 3H), 7.38-7.41 (dd, 1H,  $J = 8.2$  Hz, 1.74 Hz), 7.49 (s, 1H), 8.12 (s,  
 1H), 10.32 (s, 1H).  $M + 1 = 573$ .

20 [0099] Example 216

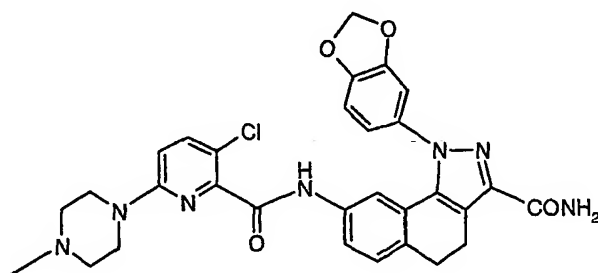
1-(1,3-benzodioxol-5-yl)-8-[[3,6-dichloropyridin-2-yl]carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



The title compound was synthesized from 1.653 g of 3,6-dichloro-2-pyridine  
 5 carboxylic acid (CP92740, prepared by the method of E. Marzi, A. Bigi, M.  
 Schlosser, *Eur. J. Org. Chem.* 2001, 1371 - 1376) and the title compound of step 4  
 of Example 161 (2.0 g) by the same procedure used for Example 211. The title  
 compound is a brown solid (2.4 g, 80%), m.p. 263-265 °C. Its structure was  
 confirmed by <sup>1</sup>H NMR and LC/MS: <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO): δ 2.82-3.01 (m, 4H),  
 6.11 (s, 2H), 6.97-7.07 (m, 2H), 7.38 d, 1H, *J* = 1 Hz), 7.81 (s, 1H), 7.33-7.42 (m,  
 10 3H), 7.52 (s, 1H), 7.51 (d, 1H, *J* = 9 Hz), 8.15 (d, 1H, *J* = 9 Hz), 10.57 (s, 1H). ESI  
 mass spectrum for C<sub>25</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>4</sub><sup>+</sup>: 522 (*M* + 1).

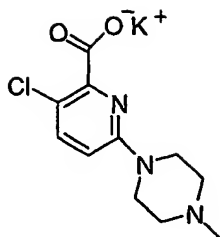
[00100] Example 217

1-(1,3-benzodioxol-5-yl)-8-((3-chloro-6-(4-methylpiperazin-1-yl)pyridin-2-  
 15 yl)carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



[00101] Step 1

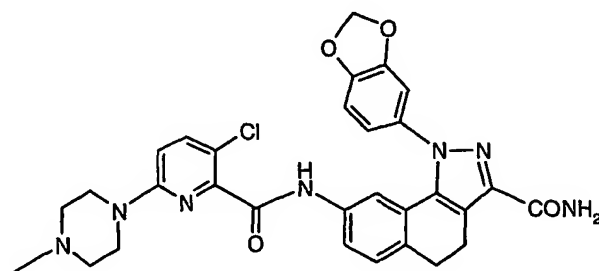
20 Potassium 3-chloro-6-(4-methylpiperazin-1-yl)pyridine-2-carboxylate



Potassium 3-chloro-6-(4-methylpiperazin-1-yl)pyridine-2-carboxylate was synthesized by the reaction used in Example 250 step 1 starting with 3,6-dichloro-2-pyridine carboxylic acid (0.60 g, 3.125 mmol) N-methylpiperazine (7.2 g, 72 mmol). The reaction was carried out at 95°C for 3 days. The volatiles were removed under vacuum. The resulting residue was washed with a saturated solution of K<sub>2</sub>CO<sub>3</sub> and with CH<sub>2</sub>Cl<sub>2</sub>. Three layers were formed. The middle was separated, dried, and the solvent was removed under reduced pressure giving 0.89 g of Potassium 3-chloro-6-(4-methylpiperazin-1-yl)pyridine-2-carboxylate (96%). Its structure was confirmed by <sup>1</sup>H NMR and LC/MS: <sup>1</sup>H NMR (D<sub>2</sub>O): δ 2.18 (s, 3H), 2.43 (s, broad, 4H), 3.37 (s, broad, 4H), 6.77 (d, 1H, J = 9 Hz), 7.58 (d, 1H, J = 9 Hz). ESI mass spectrum for C<sub>11</sub>H<sub>15</sub>ClN<sub>3</sub>O<sub>2</sub><sup>+</sup>: 256 (M + 1) in the presence of TFA.

#### [00102] Step 2

1-(1,3-benzodioxol-5-yl)-8-([3-chloro-6-(4-methylpiperazin-1-yl)pyridin-2-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



The title compound was synthesized from 0.30 g of 3-chloro-6-(4-methylpiperazin-1-yl)-2-pyridine carboxylic acid, obtained by acidification of its K-salt from step 1, and the title compound of step 4 of Example 161 (0.217 g) by the same procedure used for Example 260. The title compound is a brown solid (0.23 g, 61%), m.p.

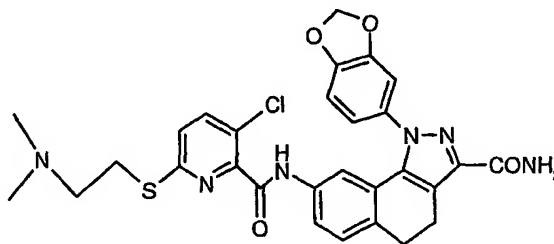
264-266° C (decomposition). Its structure was confirmed by <sup>1</sup>H NMR and LC/MS: <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO): δ 2.70 (s, 3H), 2.72-4.30 (m, 12H), 6.02 (s, 2H), 6.92-7.12 (m, 4H), 7.22-7.36 (m, 3H), 7.42-7.53 (m, 2H), 7.77 (d, 1H, *J* = 9 Hz), 10.32 (s, 1H). ESI mass spectrum for C<sub>30</sub>H<sub>29</sub>ClN<sub>7</sub>O<sub>4</sub><sup>+</sup>: 586 (*M* + 1).

5

**[00103] Example 218**

1-(1,3-benzodioxol-5-yl)-8-[[[(3-chloro-6-{{2-(dimethylamino)ethyl}thio}pyridin-2-yl)carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

10



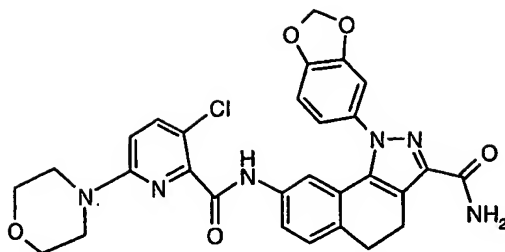
The title compound was synthesized from 0.36 g of the title compound of step 1 of Example 262, and the title compound of step 4 of Example 161 (0.35 g) by the same procedure used for Example 260. The title compound is a white solid (0.51 g, 86%). Its structure was confirmed by <sup>1</sup>H NMR and LC/MS: <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO): δ 2.18 (s, 6H), 2.55 (m, 2H), 2.85 (m, 4H), 3.24 (m, 2H), 6.10 (s, 2H), 6.90-7.08 (m, 2H), 7.14 (s, 1H), 7.22-7.35 (m, 2H), 7.36-7.47 (m, 3H), 7.52 (s, 1H), 7.84 (d, 1H, *J* = 9 Hz), 10.40 (s, 1H). ESI mass spectrum for C<sub>29</sub>H<sub>28</sub>ClN<sub>6</sub>O<sub>4</sub>S<sup>+</sup>: 591 (*M* + 1).

20

**[00104] Example 219**

1-(1,3-benzodioxol-5-yl)-8-[[[(3-chloro-6-morpholin-4-yl)pyridin-2-yl)carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

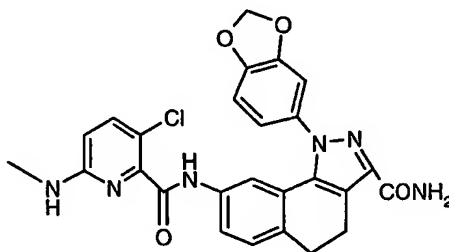




The title compound was synthesized from 0.27 g of morpholine and the title compound of Example 216 (0.522 g) by the same procedure used for Example 207 except that EtOH was replaced by 0.5 ml of DMA. The reaction was carried out at 80°C for 36 hours. The title compound, isolated by preparative HPLC, is a white solid (0.30 g, 52%), m.p. 260-262°C (decomposition). Its structure was confirmed by <sup>1</sup>H NMR and LC/MS: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.96 (m, 2H), 3.15 (m, 2H), 3.48 (m, 4H), 3.86 (m, 4H), 5.41 (s, 1H), 6.74-6.86 (m, 2H), 6.90-7.04 (m, 2H), 7.16 (d, 1H, *J* = 1 Hz), 7.28-7.35 (m, 2H), 7.54-7.22 (m, 2H), 9.32 (s, 1H). ESI mass spectrum for C<sub>29</sub>H<sub>26</sub>ClN<sub>6</sub>O<sub>5</sub><sup>+</sup>: 573 (M + 1).

**[00105] Example 220**

1-(1,3-benzodioxol-5-yl)-8-({[3-chloro-6-(methylamino)pyridin-2-yl]carbonyl}amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



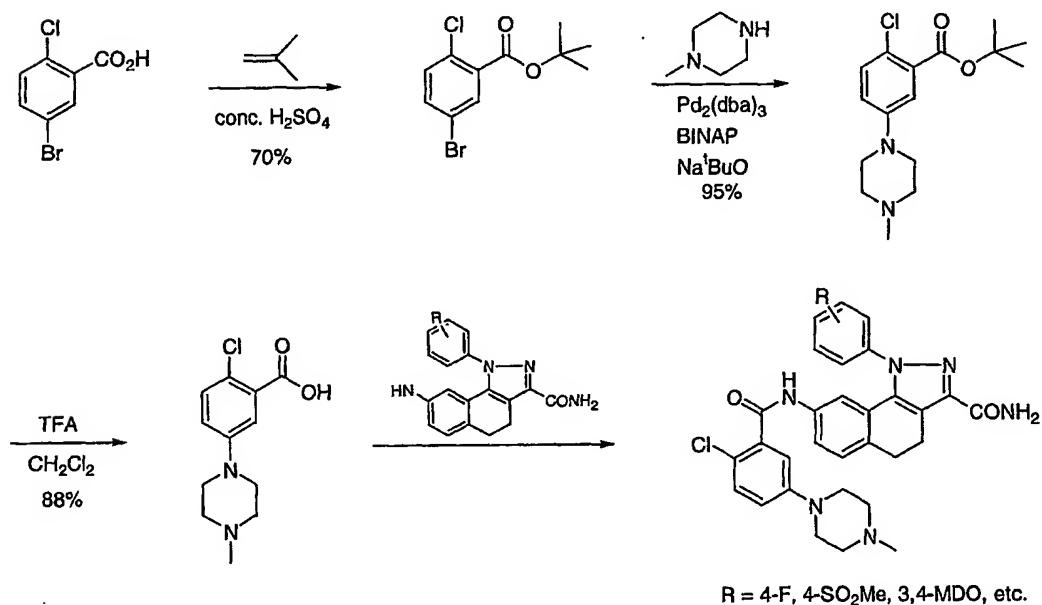
The title compound was synthesized from N-methylamine (6 mL of 33 w% solution in EtOH) and the compound of Example 216 (1.04 g) by the same procedure used for Example 207 except that 1 mL of DMA was added. The reaction was carried out at 82°C for 5 days. The title compound, isolated by preparative HPLC, is a white solid (0.29 g, 52%), M.p. 269-270°C (decomposition). Its structure was

confirmed by  $^1\text{H}$  NMR and LC/MS:  $^1\text{H}$  NMR ( $d_6$ -DMSO):  $\delta$  2.76 (d, 3H,  $J = 5.5$  Hz), 2.84-3.99 (m, 4H), 6.16 (s, 2H), 6.57 (d, 1H,  $J = 9$  Hz), 6.91-7.04 (m, 3H), 7.12 (d, 1H,  $J = 1$  Hz), 7.22-7.34 (m, 3H), 7.46-7.54 (m, 3H), 10.19 (s, 1H). ESI mass spectrum for  $\text{C}_{26}\text{H}_{22}\text{ClN}_6\text{O}_4^+$ : 517 ( $M + 1$ ).

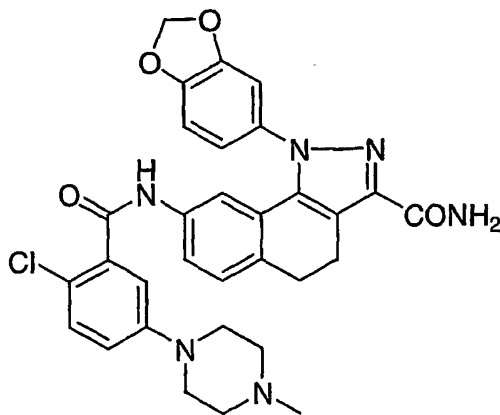
5

## [00106] Example 221

## SCHEME XXIV



10



[00107] Step 1: A solution of 2-chloro-5-bromobenzoic acid (23.6 g, 0.1 mol), conc. sulfuric acid (5 mL) and condensed isobutene (400 mL) was prepared in a pressure vessel and stirred at room temperature under 12 psi for 2 days. The vessel was opened and the excess isobutene was released. The remaining liquid was treated with sat. NaHCO<sub>3</sub> solution and extracted with methylene chloride. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and filtered. The filtrate was concentrated in vacuum to give 20.5 g of the crude product as brown oil, which was used without further purification (70%).

10 [00108] Step 2: A mixture of *tert*-butyl 2-chloro-5-bromobenzoate (2.95 g, 0.01 mol), N-methylpiperazine (1.5 g, 0.015 mol), Na<sup>t</sup>BuO (1.5 g, 0.015 mol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.18 g, 0.0002 mol) and BINAP (0.2 g, 0.0003 mol) in toluene was heated at 100°C under nitrogen for 16 h. The solution was cooled to room temperature and filtered through a pad of Celite®. The filtrate was concentrated and the residue was partitioned between methylene chloride and water. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and filtered. The filtrate was concentrated in vacuum to give 3.0 g of the crude product as a dark brown oil (97%). The NMR and MS were consistent with the proposed structure.

20 [00109] Step 3: To a solution of *tert*-butyl 2-chloro-5-(4-methylpiperazin-1-yl)benzoate (7.3 g, 0.023 mol) in methylene chloride (150 mL) was added trifluoroacetic acid (62 mL, 0.8 mol) dropwise at 0-5°C. The reaction mixture was stirred overnight while allowing to warm up to room temperature. Solvent and excess TFA was removed and the residue was triturated with ether to give 7.5 g of acid as a light brown solid; <sup>1</sup>H NMR (DMSO, 400 MHz) δ: 10.11 (s, 1H), 7.39 (d, J = 8.9 Hz, 1H), 7.33 (d, J = 3.1 Hz, 1H), 7.16 (dd, J = 3.1, 8.9 Hz, 1H), 3.90 (d, J = 12.2 Hz, 2H), 3.52 (d, J = 11.1 Hz, 2H), 3.15 (m, 2H), 2.98 (m, 2H), 2.87 (s, 3H); Anal. Calcd. for C<sub>12</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>2</sub> + 1.0 TFA: C, 45.60; H, 4.37; N, 7.60. Found: C, 45.99; H, 4.62; N, 7.21.

30

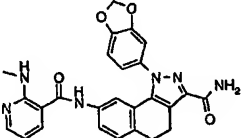
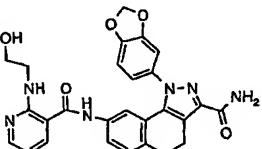
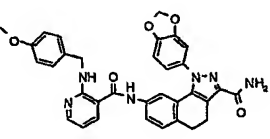
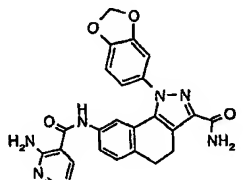
[00110] Step 4: To a mixture of 2-chloro-5-(4-methylpiperazin-1-yl)benzoic acid (0.9 g, 0.0035 mol), the title compound of step 4 of Example 161 (0.82 g,

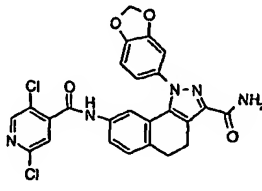
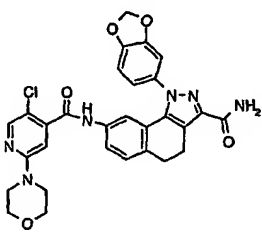
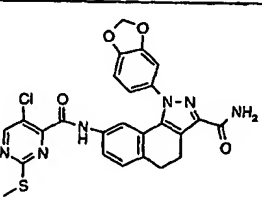
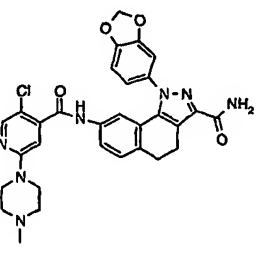
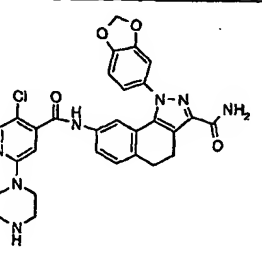
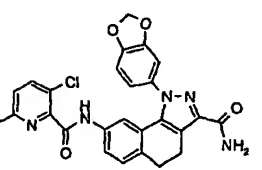
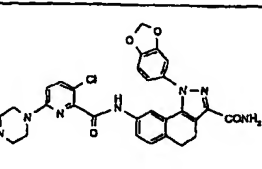
0.0024 mol) and 1 mL of diisopropylethylamine in 25 mL of DMF was added HATU (1.3 g, 0.0035 mol) in one portion. The reaction mixture was stirred at room temperature for 16 h. Solvent was removed and the residue was purified on preparative HPLC to give 1.25 g of the product as a pale white solid (89% yield);  
 5 mp: 185-187°C; <sup>1</sup>HNMR (DMSO + TFA-d, 400 MHz) δ: 10.26 (s, 1H), 9.81 (brs, 1H), 7.52 (brs, 1H), 7.44 (dd, J = 2.0, 8.1 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.30 (s, 1H), 7.12 (d, J = 2.0 Hz, 1H), 7.09 (m, 2H), 7.03 (d, J = 8.2 Hz, 1H), 6.98 (dd, J = 2.1, 8.2 Hz, 1H), 6.11 (s, 2H), 3.90 (m, 2H), 3.50 (m, 2H), 3.14 (m, 2H), 2.96 (m, 6H), 2.86 (s, 3H).

10

[00111] The bioactivity in the IKK2 Resin assay for the compounds of Examples 207-221 is shown in Table 5.

Table 5

Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin Avg. IC50 (uM)	Example
	482.50	1-((2-((2-((1,3-benzodioxol-5-yl)-8-yl)carbonyl)amino)pyridin-3-yl)carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	207
	512.53	1-((2-((2-((2-hydroxyethyl)amino)pyridin-3-yl)carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	208
	588.63	1-((2-((2-((4-methoxybenzyl)amino)pyridin-3-yl)carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	10 ≤ 100 μM	209
	468.48	8-(((2-aminopyridin-3-yl)carbonyl)amino)-1-((1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	210

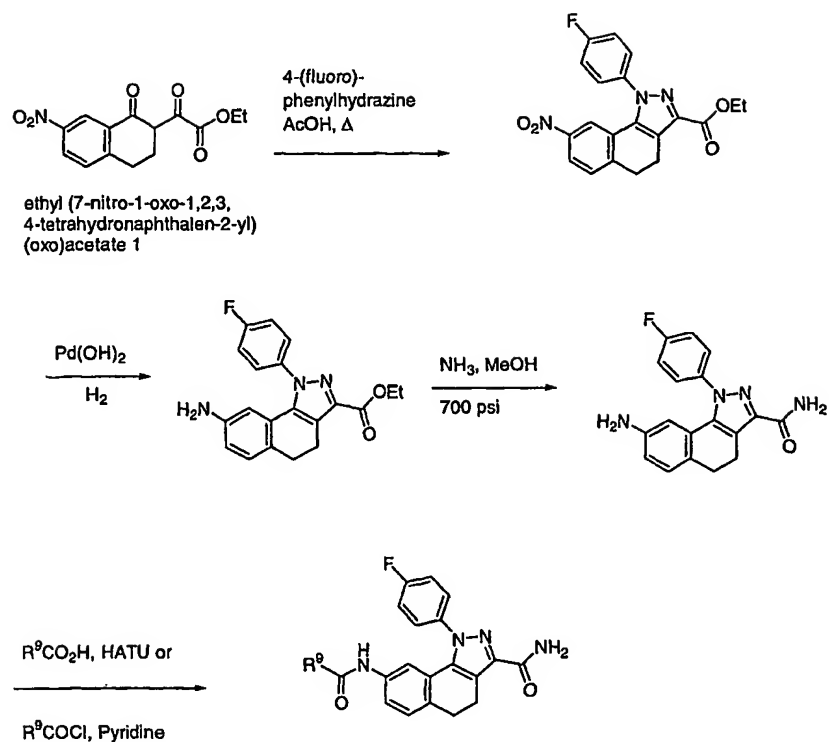
	522.35	1-(1,3-benzodioxol-5-yl)-8-[(2,5-dichloroisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	211
	573.01	1-(1,3-benzodioxol-5-yl)-8-[(5-chloro-2-morpholin-4-ylisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	212
	534.99	1-(1,3-benzodioxol-5-yl)-8-[(5-chloro-2-(methylthio)pyrimidin-4-yl)carbonyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	213
	586.06	1-(1,3-benzodioxol-5-yl)-8-[(5-chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	214
	572.03	1-(1,3-benzodioxol-5-yl)-8-[(5-chloro-2-piperazin-1-ylisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	215
	522.35	1-(1,3-benzodioxol-5-yl)-8-[(3,6-dichloropyridin-2-yl)carbonyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	216
	586.06	1-(1,3-benzodioxol-5-yl)-8-[(3-chloro-6-(4-methylpiperazin-1-yl)pyridin-2-yl)carbonyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	217

	591.09	1-((3-chloro-6-((2-(dimethylamino)ethyl)thio)pyridin-2-yl)carbonylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	218
	573.01	1-((3-chloro-6-morpholin-4-yl)pyridin-2-yl)carbonylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	219
	516.95	1-((3-chloro-6-(methylamino)pyridin-2-yl)carbonylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	220
	585.07	1-((2-chloro-5-(4-methylpiperazin-1-yl)benzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	221

**[00112]**      Examples 222-243

- 5      Examples 222-243 shown in Table 6 were synthesized with the corresponding starting compounds using the following synthesis procedure similar to Scheme I where R<sup>9</sup> is the appropriate aryl, substituted aryl, heteroaryl, substituted heteroaryl, substituted arylalkyl, substituted heteroarylalkyl, or cycloalkyl.

## [00113] SCHEME XXV



5

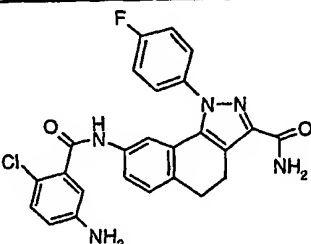

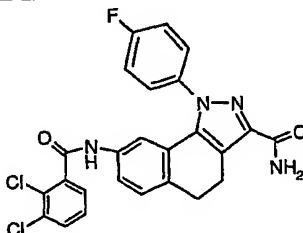
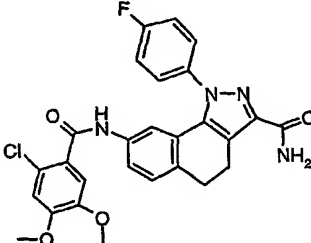
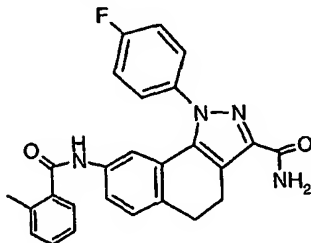
Table 6

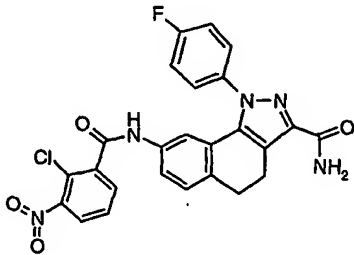
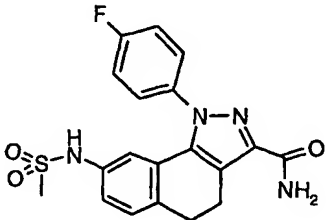
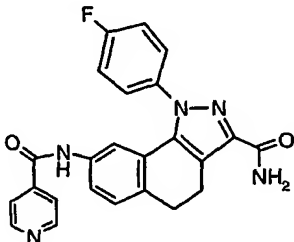
Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC <sub>50</sub> (	Example
	522.99	8-[[2-chloro-5-(methylsulfinyl)benzoyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	222
	496.33	8-[[[(2,5-dichloropyridin-3-yl)carbonyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	223

Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50 (	Example
	504.90	8-([(6-chloro-1,3-benzodioxol-5-yl)carbonyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	224
	461.88	8-([(2-chloropyridin-3-yl)carbonyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	225
	538.99	8-([(2-chloro-4-(methylsulfonyl)benzoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	226
	475.91	8-([(2-chloro-6-methylpyridin-3-yl)carbonyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	227
	498.35	8-([(3-chloroisonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$\leq 1 \mu\text{M}$	228
	475.91	8-([(3-amino-2-chlorobenzoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	229



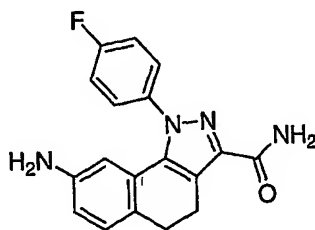
Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50 (	Example
	460.90	8-[(2-chlorobenzoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	230
	456.48	1-(4-fluorophenyl)-8-[(3-hydroxy-2-methylbenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	231
	475.91	8-[(4-amino-2-chlorobenzoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	232
	490.92	8-[(2-chloro-4-methoxybenzoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	233
	529.88	8-[(2-chloro-6-(trifluoromethyl)pyridin-3-yl)carbonyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	234
	506.99	8-[(2-chloro-5-(methylthio)benzoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	235

Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50 (	Example
	475.91	8-[(5-amino-2-chlorobenzoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	236
	503.97	8-[(2-chloro-5-(dimethylamino)benzoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	237
	495.34	8-[(2,3-dichlorobenzoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	238
	520.95	8-[(2-chloro-4,5-dimethoxybenzoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	239
	440.48	1-(4-fluorophenyl)-8-[(2-methylbenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	240

Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50 (	Example
	505.89	8-[(2-chloro-3-nitrobenzoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	241
	400.43	1-(4-fluorophenyl)-8-[(methylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	242
	427.44	1-(4-fluorophenyl)-8-(isonicotinoylamino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	243

**[00114]** Example 244

8-amino-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

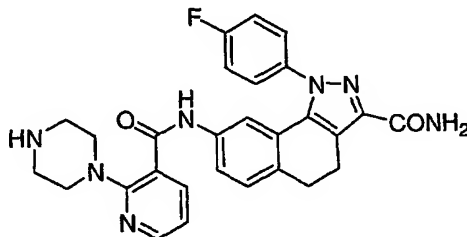


This material was prepared from 4-fluorophenyl hydrazine by the method described for  
 5 Example 92.

**[00115]** Example 245

1-(4-fluorophenyl)-8-{[(2-piperazin-1-ylpyridin-3-yl)carbonyl]amino}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

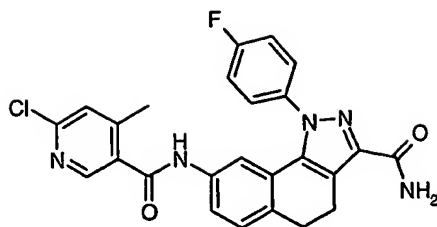
10



The title compound was synthesized by the same procedure as in Example 207 starting with the title compound of Example 225 (0.81 g, 0.017 mol) and piperazine (3 g, 0.0348 mol) in 4 mL Et OH to afford 0.523 g of title compound (yield: 58 %). Mp: 156-157 °C.  
 15 <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): δ 2.63 (t, 4H, *J* = 4.5 Hz), 2.86-2.93 (m, 4H), 3.08 (t, 4H, *J* = 4.5 Hz), 6.86-6.90 (dd, 1H, *J* = 7.4 Hz, 4.8 Hz), 7.23 (s, 1H), 7.28 (s, 1H), 7.32 (d, 1H, *J* = 8.3 Hz), 7.40 (t, 2H, *J* = 8.7 Hz), 7.54-7.6 (m, 4H), 7.63-7.66 (dd, 1H, *J* = 7.4 Hz, 1.7 Hz), 8.22-8.25 (dd, 1H, *J* = 4.8 Hz, 1.9 Hz), 10.25 (s, 1H). *M* + 1 = 512.

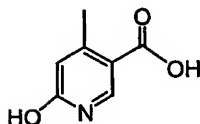
**[00116]** Example 246

8-{[(6-chloro-4-methylpyridin-3-yl)carbonyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



[00117] Step 1

6-Hydroxy-4-methylnicotinic acid



5

A modification of the procedure of Weglinski and Talik (*Rocz. Chem.* 1977, 51, 2401) was used. Potassium carbonate powder (-325 mesh) was dried under vacuum at 200 °C overnight prior to use. A layer of the dried potassium carbonate (28.56 g, 0.207 mol) was placed in the bottom of a 300-mL Hastelloy-B autoclave followed by a layer of 2-hydroxy-4-methylpyridine (28.51 g, 0.2612 mol) mixed with dried potassium carbonate (28.70 g, 0.208 mol). The vessel was sealed, carefully purged with dry carbon dioxide (5 x 80 psig), pressurized with dry carbon dioxide to 800 psig, and heated to 130 °C for 18 h. After cooling and careful venting, the product mixture was dissolved in water (560 mL) and added to 132 mL of 6 N HCl with vigorous stirring over about 20 min. The pH of the resulting slurry was 2.43 and potassium carbonate (ca. 0.25 g) was added to pH=2.53. After stirring the slurry for 1 h at 25 °C, the precipitate was recovered by vacuum filtration, washed with water (3 x 35 mL), and dried in vacuo at 100 °C to afford 7.11 g of a tan powder. <sup>1</sup>H NMR analysis of the tan powder was consistent with a mixture of about 5.6 mol% 2-hydroxy-4-methylpyridine and 94.4 mol% of the desired 2-hydroxy-4-methyl-5-pyridinecarboxylic acid. The yield was estimated to be 17.0% based on the NMR assay of the recovered product. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO) δ 2.36 (d, *J* = 1 Hz, 3H), 6.19 (apparent s, 1H), 7.99 (s, 1H), 12.2 (broad s, 2H). <sup>13</sup>C NMR (100 MHz, *d*<sub>6</sub>-DMSO) δ 21.6, 109.1, 119.5, 141.1, 151.8, 161.8, 165.8.

10

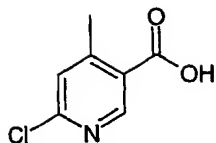
15

20

25

[00118] Step 2

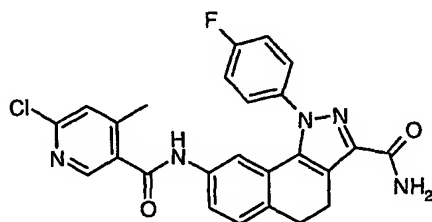
## 4-Methyl-6-chloronicotinic acid



6-Hydroxy-4-methylnicotinic acid (10 g, 65.3 mmol) and phosphorus oxychloride (33 mL) were combined and refluxed for 3 hours. The reaction solution was poured into 300 mL of ice and then 600 mL of water was added. The solution was boiled for 30 minutes before cooling and extracting the product into ether. The solvent was removed and the residue was recrystallized from 900 mL of hot water. Yellow solid, 9.06g (81% yield). Mp 170-172 °C. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 2.61 (s, 3H), 7.41 (s, 1H), 8.80 (s, 1H). LC-MS, M + 1 = 172.

## [00119] Step 3

8-[[[(6-chloro-4-methylpyridin-3-yl)carbonyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

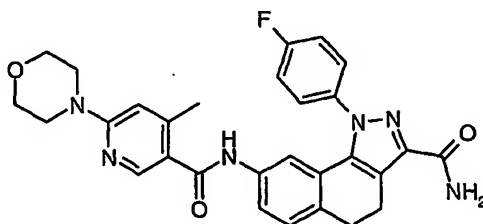


The compound of example 244 (3.872 mmoles), 4-methyl-6-chloronicotinic acid from step 2 (5.828 mmoles), and HATU (5.844 mmoles) were dissolved in 20 mL DMF followed by the addition of 1.9 mL triethylamine. The mixture was stirred at room temperature overnight. The solvent was then stripped and the residue suspended in water, filtered, and washed with water. The solid was recrystallized from acetonitrile, then redissolved in acetonitrile, decolorized with decolorizing carbon, and dried over anhydrous MgSO<sub>4</sub>. The solvent was then stripped down to a solid. Mp: 280-284°C. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 400 MHz): δ 2.28 (s, 3H); 2.84-2.98 (m, 4H); 7.25-7.44 (m, 6H); 7.49 (s, 1H); 7.51-7.62 (m, 3H); 8.35 (s, 1H); 10.31 (s, 1H). <sup>13</sup>C NMR (DMSO, 100 MHz): δ 19.13, 20.35, 29.67, 115.01, 117.07, 117.30, 120.08, 121.34, 126.19, 126.60, 128.72, 128.81, 129.58, 132.80,

133.42, 136.81, 136.84, 137.64, 139.71, 143.19, 148.42, 149.96, 151.59, 161.44, 163.88, 164.47, 164.78.  $M + 1 = 476$ .

**[00120] Example 247**

- 5 1-(4-fluorophenyl)-8-[[[4-methyl-6-morpholin-4-ylpyridin-3-yl]carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

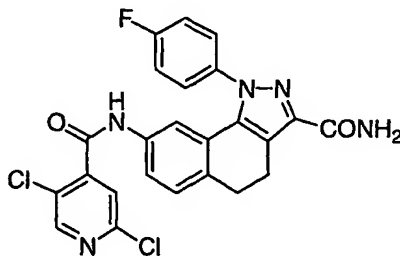


The title compound of Example 246 (1.47 mmoles) and morpholine (23.1 mmoles) were dissolved in 10 mL of *N,N*-dimethylacetamide. The reaction mixture was then placed  
 10 under nitrogen and stirred in an oil bath at 100°C for 27 h. The mixture was partially stripped of solvent then added to water, filtered, and washed with water. The solid was recrystallized from acetonitrile, then dissolved in acetonitrile and dried over anhydrous  $MgSO_4$ . The solvent was then stripped down to a solid. Mp: 301°C (decomp.)  $^1H$  NMR ( $d_6$ -DMSO, 400 MHz):  $\delta$  2.22 (s, 3H); 2.80-2.94 (m, 4H); 3.46 (t, 4H,  $J = 4.8$  Hz); 3.62 (t, 4H,  $J = 4.8$  Hz); 6.67 (s, 1H); 7.22-7.27 (m, 3H); 7.31-7.38 (m, 2H); 7.42 (dd, 1H,  $J = 1.9$ Hz, 8.2Hz); 7.49-7.57 (m, 3H); 8.11 (s, 1H); 9.92 (s, 1H).  $^{13}C$  NMR ( $d_6$ -DMSO, 100 MHz):  $\delta$  20.35, 20.38, 29.63, 45.55, 66.54, 108.46, 114.91, 117.02, 117.25, 119.91, 121.23, 122.78, 126.42, 128.64, 128.73, 129.36, 132.60, 136.82, 136.85, 138.38, 139.82, 143.15, 147.70, 148.03, 160.04, 161.39, 163.84, 164.47, 166.18.  $M + 1 = 527$

20

**[00121] Example 248**

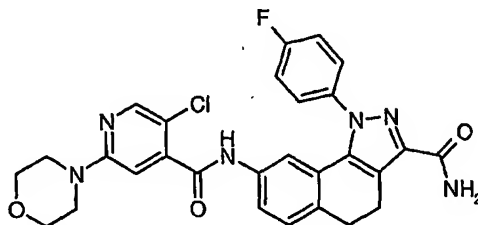
8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



2,5-Dichloroisonicotinic acid (1.65g, 0.0086 mol), HATU (3.27g, 0.0086 mol), and Et<sub>3</sub>N (2.32 mL, 0.0166 mol) were added to a solution of the title compound of Example 244 (1.85g, 0.00574 mol) in 29 mL of DMF. The reaction mixture was stirred at room temperature for 3 h. The completion of the reaction was confirmed by monitoring the disappearance of the title compound of Example 246 step 2 in LC/MS. The crude reaction mixture was concentrated to about 10 mL of DMF. Upon addition of water to this DMF residue, a white solid was formed. This white solid was triturated in water for 20 min and filtered. The solid was collected, dissolved in THF, and dried with MgSO<sub>4</sub>. Removal of the solvent afforded a brown solid that was crystallized from CH<sub>3</sub>CN to give 2.1 g of the title compound as white needles (yield 73%). <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): 2.86-2.91 (m, 4H), 7.18 (d, 1H, *J* = 1.2 Hz), 7.25 (s, 1H), 7.32-7.36 (m, 4H), 7.52-7.56 (m, 3H), 7.75 (s, 1H), 8.57 (s, 1H), 10.49 (s, 1H). *M* + 1 = 497.

15 [00122] Example 249

8-[(5-chloro-2-morpholin-4-ylisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



20 The title compound of Example 244 (0.757 mmoles), 5-chloro-2-morpholin-4-ylisonicotinic acid, (1.38 mmoles), and HATU (1.57 mmoles) were dissolved in 5 mL DMF followed by the addition of 0.4 mL of triethylamine. The mixture was stirred at room temperature for 3 hrs and partially stripped of DMF. The reaction mixture was then added to water, filtered, and washed with water. The solid was dissolved in THF, decolorized with decolorizing carbon, and dried over anhydrous MgSO<sub>4</sub>. The THF was stripped and the solid triturated in diethyl ether three times, then triturated in ethanol, and twice more with acetonitrile, filtered and dried under vacuum. Mp: 309-313°C. <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO, 400 MHz): δ 2.80-2.95 (m, 4H); 3.42 (t, 4H, *J* = 5 Hz); 3.62 (t, 4H, *J* = 5 Hz); 6.88 (s,

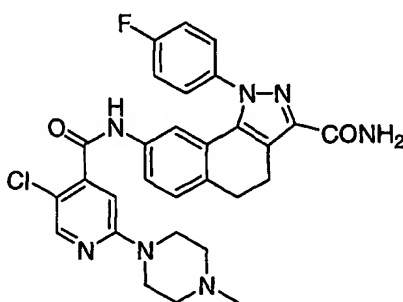


1H); 7.17-7.21 (m, 1H); 7.23-7.41 (m, 5H); 7.49-7.58 (m, 3H); 8.14 (s, 1H); 10.31 (s, 1H).  
<sup>13</sup>C NMR (d<sub>6</sub>-DMSO, 100 MHz): δ 20.34, 29.70, 45.74, 66.50, 106.55, 114.97, 115.87, 117.09, 117.32, 120.05, 121.41, 126.67, 128.64, 128.73, 129.62, 133.47, 136.80, 136.82, 137.48, 139.64, 143.21, 145.28, 147.54, 158.30, 161.39, 163.85, 164.45. M + 1 = 547.

5

[00123] Example 250

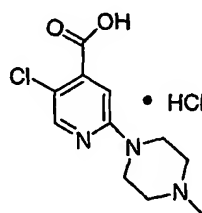
8-[[5-chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino]-1-(4-fluorophenyl)-  
 4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



10

[00124] Step 1

5-chloro-2-(4-methylpiperazin-1-yl)isonicotinic acid hydrochloride



15

5-chloro-2-(4-methylpiperazin-1-yl)isonicotinic acid hydrochloride was synthesized by the same procedure as for example 212 step 1 starting with 2,5-dichloroisonicotinic acid (3 g, 0.0156 mol) N-methylpiperazine (30.7g, 0.30 mol) in 10 mL of N,N-dimethylacetamide. The reaction was carried out at 100°C for 8 days. The volatiles were removed under vacuum. The resulting residue was washed with a saturated solution of K<sub>2</sub>CO<sub>3</sub> and with CH<sub>2</sub>Cl<sub>2</sub>. The solvents were removed under vacuum and the resulting residue dissolved in the minimum amount of water, acidified to pH = 1 with an aqueous solution of HCl (1N) and washed with CH<sub>2</sub>Cl<sub>2</sub>. Upon standing at room temperature, the acidic aqueous layer

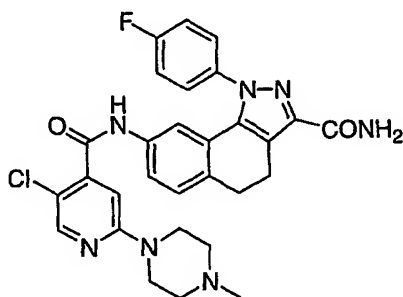
20

afforded 2g (yield: 44%) of title compound.  $^1\text{H}$  NMR (300 MHz,  $\text{D}_2\text{O}$ ):  $\delta$  2.85 (s, 3H), 3.13 (t, 2H,  $J = 12.28$  Hz), 3.34 (t, 2H,  $J = 14.3$  Hz), 3.56 (d, 2H,  $J = 12.28$  Hz), 4.18 (d, 2H,  $J = 14.3$  Hz), 7.08 (s, 1H), 8.00 (s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{D}_2\text{O}$ ):  $\delta$  43.1, 43.4, 52.54, 109.5, 117.6, 142.3, 147.9, 154.4, 169.5.

5

[00125] Step 2

8-[[5-chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



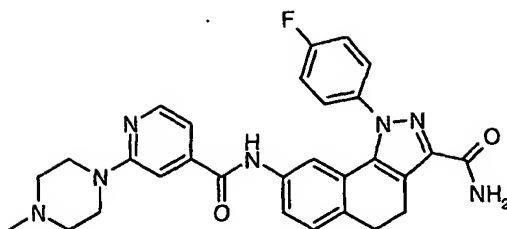
10

The title compound was synthesized by the same procedure as in Example 211 starting with 5-chloro-2-(N-methyl-piperazinyl)isonicotinic acid hydrochloride from step 1)) (0.59 g, 0.00202 mol), the title compound of Example 244 (0.432 g, 0.00134 mol), HATU (0.755g, 0.00198mol) and  $\text{Et}_3\text{N}$  (1.09 mL, 0.0078 mol) in DMF (8 mL) to yield 0.305 g of the title compound (yield: 40%).  $^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO):  $\delta$  2.17 (s, 3H), 2.33 (t, 4H,  $J = 4.8$  Hz), 2.87-2.93 (m, 4H), 3.47 (t, 4H,  $J = 4.8$  Hz), 6.87 (s, 1H), 7.2 (d, 1H,  $J = 1.9$  Hz), 7.27 (s, 1H), 7.29-7.41 (m, 5H), 7.53-7.58 (m, 3H), 8.13 (s, 1H), 10.31 (s, 1H).  $M + 1 = 561$ .

20

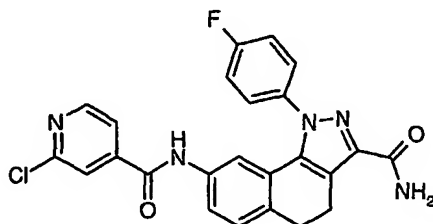
[00126] Example 251

1-(4-fluorophenyl)-8-[[2-(4-methylpiperazin-1-yl)isonicotinoyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



[00127] Step 1

8-[(2-chloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-  
5 benzo[g]indazole-3-carboxamide



This material was prepared from Example 244 (8-amino-1-(4-fluorophenyl)-4,5-dihydro-  
10 1H-benzo[g]indazole-3-carboxamide) and 2-chloroisonicotinic acid by the method  
described for Example 246 step 3.

[00128] Step 2

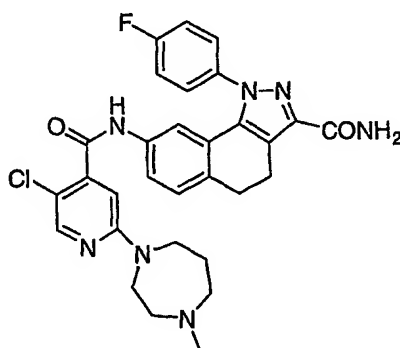
15 The material from step 1 (2.17 mmol) and N-methyl piperazine (32.9 mmol) were  
dissolved in 5.0 mL N,N-dimethylacetamide. The reaction mixture was then placed under  
nitrogen and stirred in an oil bath at 100°C for 88 h. The mixture was partially stripped of  
solvent then added to water, filtered, and washed with water. The solid was then dissolved  
in acetonitrile, decolorized with decolorizing carbon, and dried over anhydrous MgSO<sub>4</sub>.  
20 The solvent was stripped, then the solid residue was recrystallized from acetonitrile. Mp:  
277-279°C. <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO): δ 2.17 (s, 3H); 2.35 (t, 4H, J = 5 Hz); 2.82-  
2.95 (m, 4H); 3.47 (t, 4H, J = 5 Hz); 6.85 (d, 1H, J = 5 Hz); 7.01 (s, 1H); 7.21-7.44 (m,

6H); 7.50-7.59 (m, 3H); 8.16 (d, 1H,  $J = 5$  Hz); 10.10 (s, 1H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 100 MHz):  $\delta$  20.32, 29.69, 45.20, 46.46, 55.00, 105.43, 111.23, 115.50, 117.07, 117.30, 120.66, 121.37, 126.54, 128.60, 128.69, 129.48, 133.36, 136.82, 136.85, 137.70, 139.71, 143.19, 144.36, 148.89, 159.88, 161.37, 163.81, 164.44, 165.15.  $M + 1 = 526$ .

5

**[00129]** Example 252

8-[[5-chloro-2-(4-methyl-1,4-diazepan-1-yl)isonicotinoyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



10

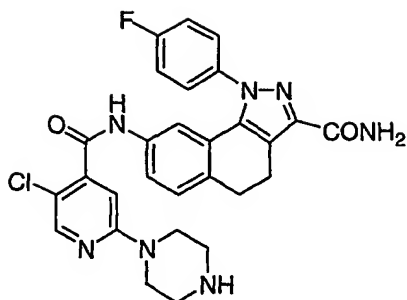
The title compound was synthesized by the same procedure as in Example 214 starting with the title compound of Example 248 (1 g, 0.0020 mol) and 1-methylhomopiperazine (4.6 g, 0.040 mol). The reaction was run at 95°C for 24 h. After allowing the reaction mixture to cool, the volatiles were removed under vacuum. The residue was triturated with

15  $\text{H}_2\text{O}$  to yield 0.899 g of the title compound as a tetrahydrate (yield: 71%).  $^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO):  $\delta$  1.81-1.83 (m, 2H), 2.21 (s, 3H), 2.41 (t, 2H,  $J = 5.5$  Hz), 2.53 (t, 2H,  $J = 4.56$  Hz), 2.87-2.93 (m, 4H), 3.53 (t, 2H,  $J = 5.5$  Hz), 3.63-3.67 (m, 2H), 6.62 (s, 1H), 7.19 (d, 1H,  $J = 1.9$  Hz), 7.27-7.38 (m, 4H), 7.42-7.45 (dd, 1H,  $J = 8.12$  Hz, 1.88 Hz), 7.53-7.58 (m, 3H), 8.07 (s, 1H), 10.31 (s, 1H).  $M + 1 = 575$ .

20

**[00130]** Example 253

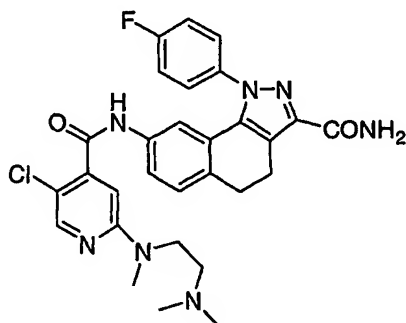
8-[(5-chloro-2-piperazin-1-ylisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



The title compound was synthesized by the same procedure as in Example 214 starting with the title compound of Example 248 (1g, 0.0020 mol) and piperazine (3.44g, 0.040 mol) in 5 mL of EtOH. The reaction was run at 100°C for 24 h. The off-white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH to afford 0.579 g of title compound (yield: 53%). <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): 2.67 (t, 4H, *J* = 4.9 Hz), 2.85-2.90 (m, 4H), 3.36 (t, 4H, *J* = 4.9 Hz), 6.80 (s, 1H), 7.18-7.19 (m, 1H), 7.25 (s, 1H), 7.27-7.35 (m, 3H), 7.37-7.39 (dd, 1H, *J* = 8 Hz, 2Hz), 7.51-7.55 (m, 3H), 8.09 (s, 1H), 10.28 (s, 1H). *M* = 1 = 547

[00131] Example 254

8-({5-chloro-2-[[2-(dimethylamino)ethyl](methyl)amino]isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[*g*]indazole-3-carboxamide

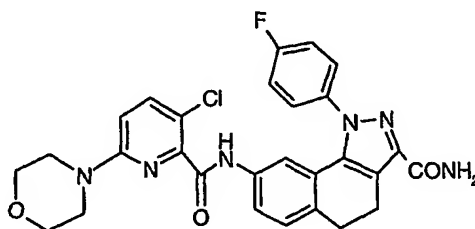


The title compound was synthesized by the same procedure as in Example 214 starting with the title compound of Example 248 (0.8 g, 0.0016 mol) and *N,N,N'*-trimethylethylene diamine (3.3 g, 0.032 mol). The reaction was run at 100°C for 24 h. After removal of the volatiles under vacuum, the residue was partitioned between water and CH<sub>2</sub>Cl<sub>2</sub>. The

organic layer was washed an additional time with water and dried over  $\text{MgSO}_4$ . The crude product mixture was purified by preparative HPLC to give 0.424 g of the title product, yield: 47%.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO): 2.13 (s, 6H), 2.34 (t, 2H,  $J = 6.7$  Hz), 2.87-2.95 (m, 4H), 2.96 (s, 3H), 3.59 (t, 2H,  $J = 6.7$  Hz), 6.58 (s, 1H), 7.2 (d, 1H,  $J = 2$  Hz),  
 5 7.27 (s, 1H), 7.29-7.37 (m, 3H), 7.41-7.44 (dd, 1H,  $J = 8$  Hz, 2 Hz), 7.53-7.58 (m, 3H), 8.13 (s, 1H), 10.36 (s, 1H).  $M + 1 = 563$ .

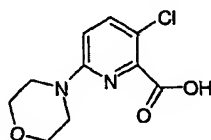
[00132] Example 255

8-[[[(3-chloro-6-morpholin-4-ylpyridin-2-yl)carbonyl]amino]-1-(4-fluorophenyl)-4,5-  
 10 dihydro-1H-benzo[g]indazole-3-carboxamide



[00133] Step 1

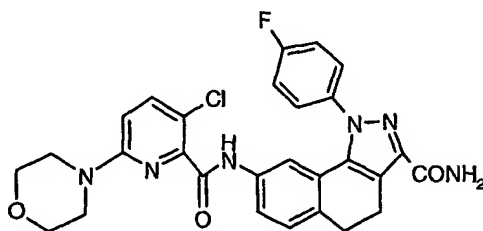
15 3-chloro-6-morpholinyl-2-pyridine carboxylic acid



3,6 Dichloropyridine-2-carboxylic acid (0.55g, 2.86 mmol), morpholine (1.37g, 15.7 mmol) and N,N dimethylacetamide (1.37 mL) were combined and stirred for 24 h at 80  
 20 °C. An additional volume of morpholine (1.39 g, 15.7 mmol) was added and heating continued for 40 hours more. After cooling the DMA was removed in the presence of toluene. The residue was dissolved in water and extracted with ether to remove excess morpholine. The aqueous was acidified to  $\text{pH} = 2$  and the product extracted into ether. Crystallization from water gave a white solid, 369 mg (53% yield).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$   
 25 3.52 (t, 4H), 3.78 (t, 4H), 6.97 (d, 1H), 7.65 (d, 1H). LC-MS,  $M + H$ : 243.

**[00134] Step 2**

8-({[3-chloro-6-morpholin-4-ylpyridin-2-yl]carbonyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



5

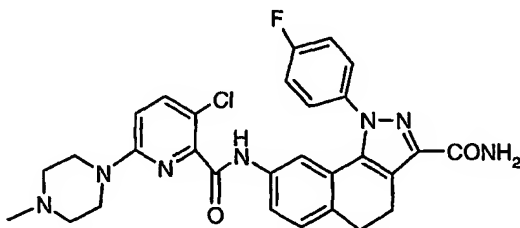
The title compound was synthesized from 0.294 g of 3-chloro-6-morpholinyl-2-pyridine carboxylic acid (from step 1) and (0.258 g) of the title compound of example 244 by the same procedure used for Example 211 except that HATU was replaced by HBTU (BF<sub>4</sub>).

10 The title compound is a brown solid (0.37 g, 84%), m.p. 252-254 °C. Its structure was confirmed by <sup>1</sup>H NMR and LC/MS: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.95 (m, 2H), 3.12 (m, 2H), 3.48 (m, 4H), 3.88 (m, 4H), 5.39 (s, 1H), 6.65-6.82 (m, 3H), 7.16 7.18-7.23 (m, 3H), 7.43-7.56 (m, 3H), 7.62 (m, 1H), 9.18 (s, 1H). ESI mass spectrum for C<sub>28</sub>H<sub>25</sub>ClFN<sub>6</sub>O<sub>3</sub><sup>+</sup>: 547 (M + 1).

15

**[00135] Example 256**

8-({[3-chloro-6-(4-methylpiperazin-1-yl)pyridin-2-yl]carbonyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



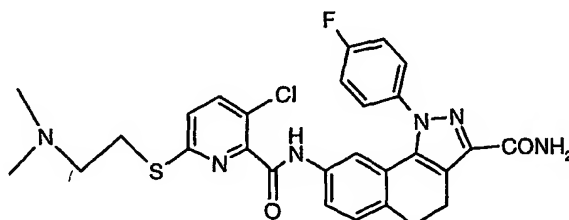
20

The title compound was synthesized from 0.501 g of 3-chloro-6-piperazinyl-2-pyridine carboxylic acid, obtained by acidification of its K-salt (from step 1 of Example 217), and the title compound of Example 244 (0.37 g) by the same procedure used for Example 217.

The title compound is a brown solid (0.56 g, 88%), m.p. 218-220°C. Its structure was confirmed by <sup>1</sup>H NMR and LC/MS: <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO): δ 2.19 (s, 3H), 2.38 (m, 4H), 2.85 (m, 4H), 3.45 (m, 4H), 6.95 (d, 1H, *J* = 9 Hz), 7.20 (d, 1H, *J* = 2 Hz), 7.26-7.40 (m, 4H), 7.49-7.62 (m, 4H), 7.63 (d, 1H, *J* = 9 Hz), 10.20 (s, 1H). ESI mass spectrum for  
 5 C<sub>29</sub>H<sub>28</sub>ClFN<sub>7</sub>O<sub>2</sub><sup>+</sup>: 560 (M + 1).

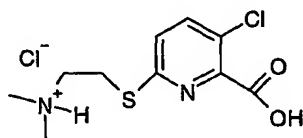
[00136] Example 257

8-[[[(3-chloro-6-[[2-(dimethylamino)ethyl]thio]pyridin-2-yl)carbonyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



[00137] Step 1

2-[(6-carboxy-5-chloropyridin-2-yl)thio]-N,N-dimethylethanaminium chloride



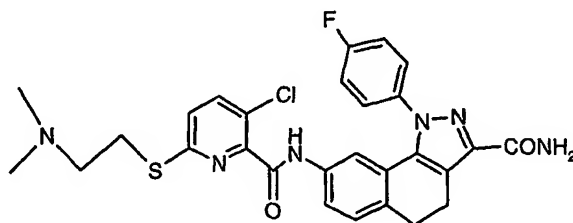
3,6-Dichloropyridine-2-carboxylic acid (1.0g, 5.23 mmol.), sodium hydroxide (1.64g, 15.7 mmol.), and anhydrous THF (10 mL) were combined before slowly adding the N,N-dimethylaminoethanethiol (1.9 g, 18.3 mmol). After stirring for several hours under nitrogen, two aliquots of DMF (10 mL each) were added. Several hours later, additional DMF (10 mL) and dimethylaminoethanethiol (1.9 g, 18.3 mmol) were added. The reaction was stirred overnight at room temperature. The solution was diluted with water and extracted three times with methylene chloride. The aqueous was acidified to pH 5 and  
 20 extracted four times with methylene chloride. The aqueous was acidified to pH 1, the  
 25 solvent was removed, and the residue was recrystallized from hot water. Yellow solid,



0.786 g (51% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  2.98 (s, 6H), 3.53 (m, 4H), 7.50 (d, 1H), 7.85 (d, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  24.4, 42.8, 58.2, 125.7, 128.1, 140.0, 147.3, 158.2, 166.0.

5 [00138] Step 2

8-[[[3-chloro-6-[[2-(dimethylamino)ethyl]thio]pyridin-2-yl]carbonyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

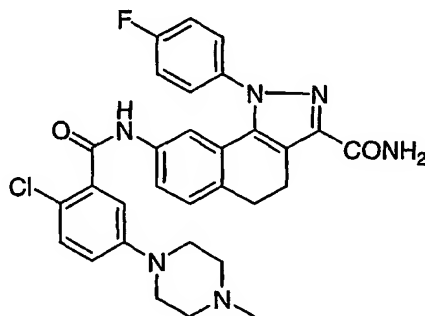


10

The title compound was synthesized from 0.355 g of the title compound of Step 1 and the title compound of Example 244 (0.32 g) by the same procedure used in Example 255. The title compound is a white solid (0.49 g, 87%). Its structure was confirmed by  $^1\text{H}$  NMR and LC/MS:  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ ):  $\delta$  2.18 (s, 6H), 2.57 (m, 2H), 2.85 (m, 4H), 3.00 (m, 4H), 3.26 (m, 2H), 5.88 (s, 1H), 6.94 (d, 1H), 7.27-7.38 (m, 5H), 7.47-7.62 (m, 3H), 7.69 (d, 1H,  $J = 9$  Hz), 9.40 (s, 1H). ESI mass spectrum for  $\text{C}_{28}\text{H}_{27}\text{ClFN}_6\text{O}_2\text{S}^+$ : 565 ( $M + 1$ ).

15

[00139] Example 258



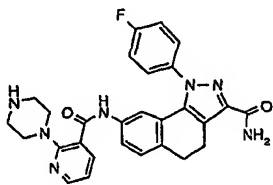
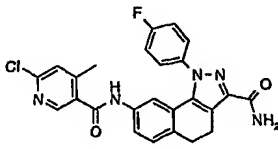
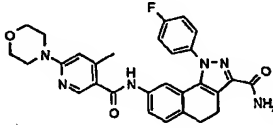
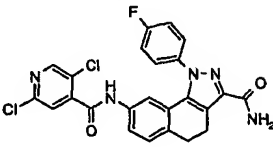
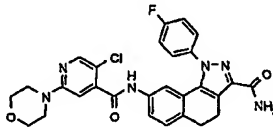
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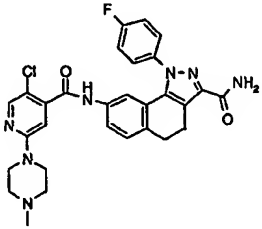
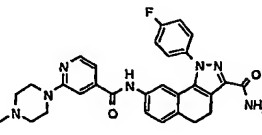
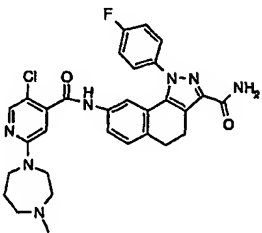
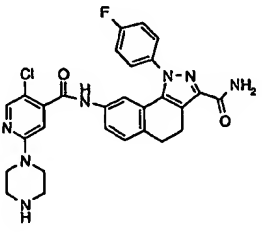
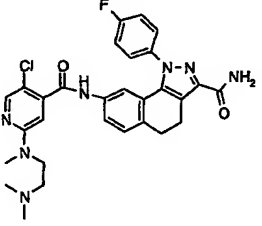
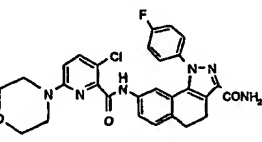
This compound was synthesized by using the same procedure described for Example 221; mp: 194-195°C;  $^1\text{H}$  NMR ( $\text{DMSO} + \text{TFA-d}$ , 400 MHz)  $\delta$ : 10.24 (s, 1H), 9.69 (s, 1H), 7.60

(m, 2H), 7.46 (d, J = 4.2 Hz, 1H), 7.38 (m, 4H), 7.10 (dd, J = 2.6, 8.9 Hz, 1H), 7.06 (s, 1H), 3.90 (d, J = 13.0 Hz, 2H), 3.50 (d, J = 12.0 Hz, 2H), 3.12 (m, 2H), 2.95 (m, 4H), 2.91 (s, 3H), 2.86 (s, 2H).

5 [00140] The IKK2 bioactivity for Examples 245-257 is shown in Table 7.

Table 7

Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	Example
	511.56	1-(4-fluorophenyl)-8-[[[(2-piperazin-1-yl)pyridin-3-yl]carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	245
	475.91	8-[[[(6-chloro-4-methylpyridin-3-yl)carbonyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	246
	526.58	1-(4-fluorophenyl)-8-[[[(4-methyl-6-morpholin-4-yl)pyridin-3-yl]carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	247
	496.33	8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	248
	546.99	8-[(5-chloro-2-morpholin-4-ylisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	249

	560.04	8-([5-chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	250
	525.59	1-(4-fluorophenyl)-8-([2-(4-methylpiperazin-1-yl)isonicotinoyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	251
	574.06	8-([5-chloro-2-(4-methyl-1,4-diazepan-1-yl)isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	252
	546.01	8-([5-chloro-2-piperazin-1-ylisonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	253
	562.05	8-([5-chloro-2-([2-(dimethylamino)ethyl](methylamino)isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	254
	546.99	8-([(3-chloro-6-morpholin-4-ylpyridin-2-yl)carbonyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	255

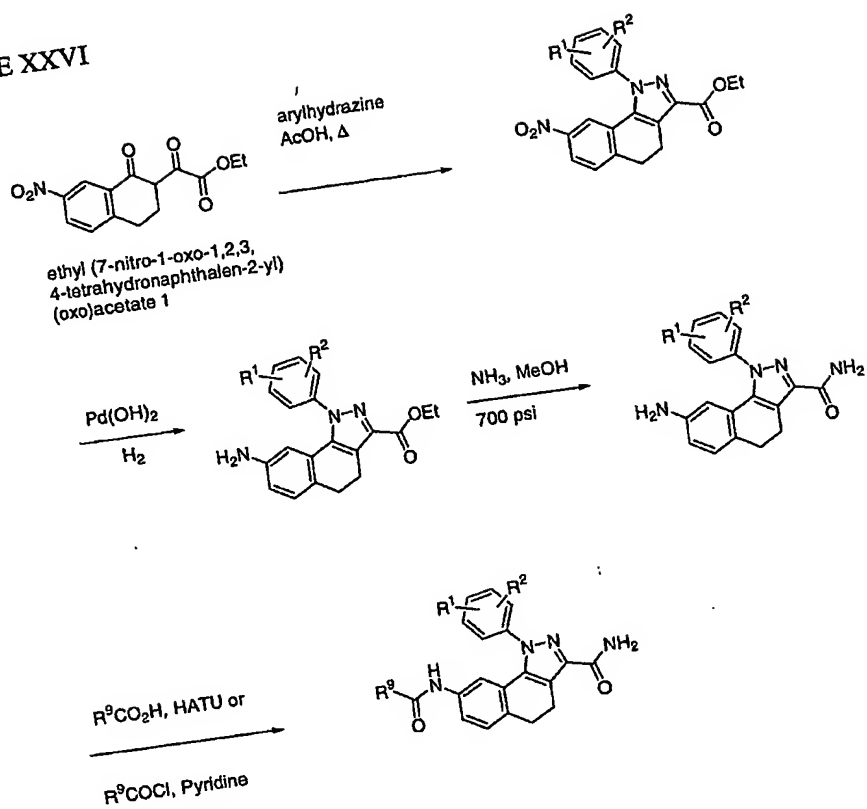
	560.04	8-({[3-chloro-6-(4-methylpiperazin-1-yl)pyridin-2-yl]carbonyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	256
	565.07	8-({[2-((dimethylamino)ethyl)thio]pyridin-2-yl]carbonyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	257
	559.05	8-({[2-chloro-5-(4-methylpiperazin-1-yl)benzoyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	258

[00141] Examples 259-263

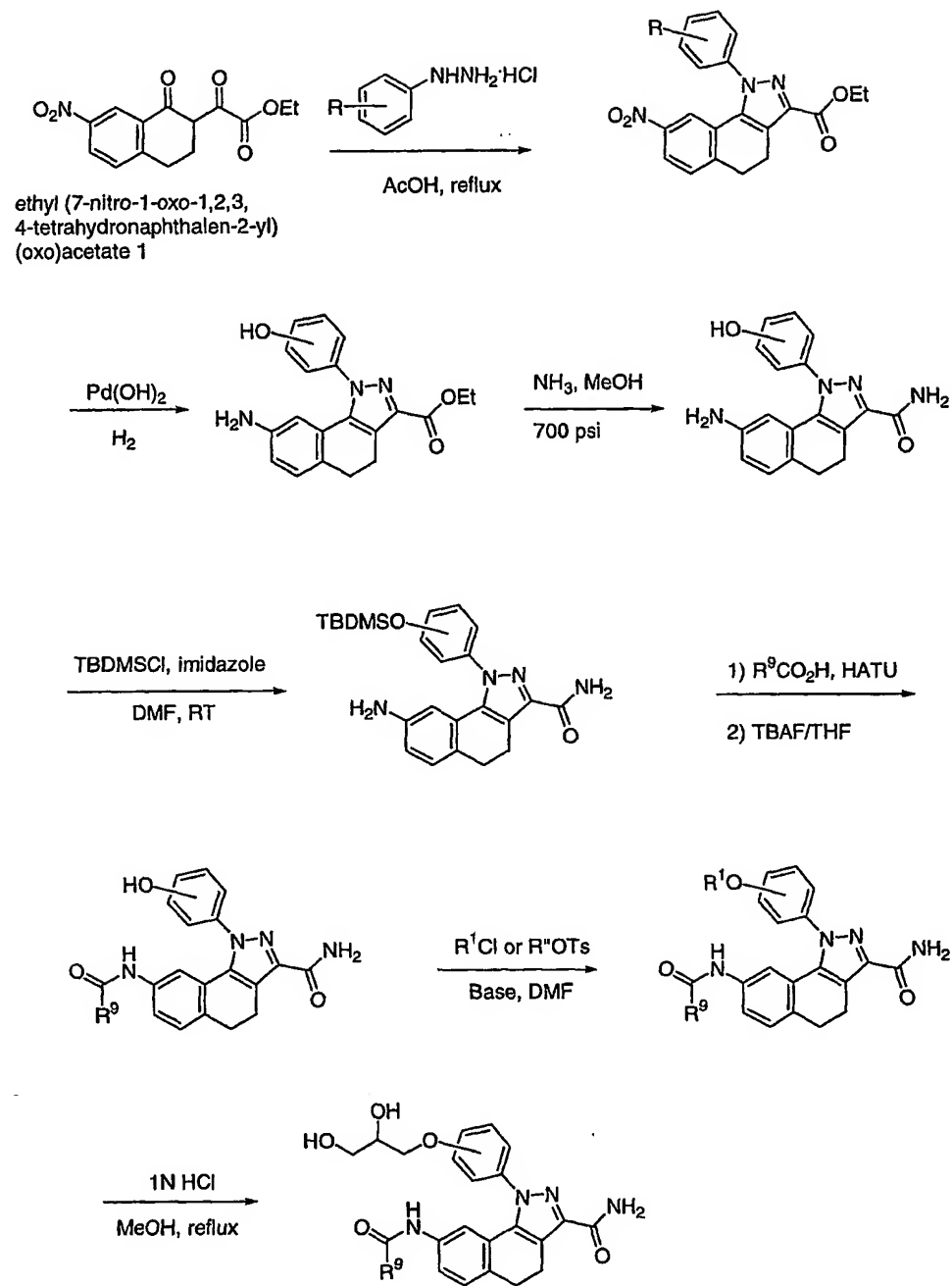
- 5 Examples 259-263 were synthesized with the corresponding starting compounds using the following synthesis procedures similar to scheme I where R<sup>9</sup> is the appropriate aryl, substituted aryl, heteroaryl, substituted heteroaryl, substituted arylalkyl, substituted heteroarylalkyl, or cycloalkyl.

14/12?PCT

## SCHEME XXVI



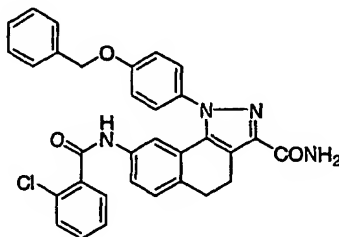
## SCHEME XXVII



R = 3- or 4-benzyloxy

**[00142] Example 259**

1-[4-(benzyloxy)phenyl]-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



5

**[00143] Step 1:** A mixture of 4-benzyloxylphenylhydrazine hydrochloride (6.42 g, 0.03 mol) and ethyl (7-nitro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)(oxo)acetate 1 (9.2 g, 0.03 mol) in 200 mL of acetic acid was refluxed for 16 h, then cooled to room temperature. The precipitate was collected by filtration and air-dried to give 8.5 g of product as a light green solid (60% yield); <sup>1</sup>HNMR (DMSO, 400 MHz) δ: 8.07 (dd, 1H), 7.66 (d, 1H), 7.35-7.53 (m, 8H), 7.24 (dd, 2H), 5.26 (s, 2H), 4.32 (q, 2H), 3.11 (m, 2H), 3.30 (m, 2H), 1.32 (t, 3H).

10

**[00144] Step 2:** A mixture of the product from step 1 (15.0 g, 0.032 mol) and tin chloride (21.6 g, 0.096 mol) in 400 mL of ethanol was heated at reflux overnight. Another two equivalent of tin chloride was added and stirred for 6 h. The reaction mixture was cooled to room temperature and the precipitate was filtered and washed with ether to give 13.5 g of the amine as a light yellow solid (96% yield); <sup>1</sup>HNMR (DMSO, 400 MHz) δ: 8.07 (dd, 1H), 7.66 (d, 1H), 7.35-7.53 (m, 8H), 7.24 (dd, 2H), 5.26 (s, 2H), 4.32 (q, 2H), 3.11 (m, 2H), 3.30 (m, 2H), 1.32 (t, 3H).

15

20

**[00145] Step 3:** A sealed reaction vessel containing the product from step 2 (6.2 g, 0.014 mol) and 40 mL of liquid ammonia in 200 mL of absolute alcohol was heated at 120°C and 600 psi for 24 h. After cooling, solvent was removed and the residue was purified by chromatography on silica gel (ethyl acetate/hexane, 6:4) to give 4.0 g of product as a pale yellow solid (70% yield); <sup>1</sup>HNMR (CDCl<sub>3</sub>, 400

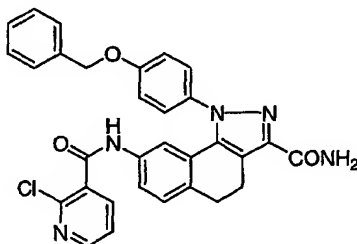
25

MHz)  $\delta$ : 7.35-7.47 (m, 7 H), 7.07 (m, 3H), 6.81 (s, 1H), 6.50 (dd, 1H), 6.07 (d, 1H), 5.49 (s, 1H), 5.15 (s, 2H), 3.37 (s, 2H), 3.08 (m, 2H), 2.86 (m, 2H).

[00146]      Step 4: To a solution of the product from step 3 (7.08 g, 0.017 mol)  
 5      in 100 mL of pyridine was added 2-chlorobenzoyl chloride (3.4 g, 0.019 mol) in one  
 portion and the reaction mixture was stirred at room temperature overnight. Solvent  
 was removed and the residue was stirred with water. The precipitate was collected  
 by filtration and air-dried to give 7.5 g of product as a white solid (80% yield);  
 $^1\text{H}$ NMR (DMSO, 400 MHz)  $\delta$ : 10.29 (s, 1H), 7.15-7.51 (m, 18 H), 5.16 (s, 2H),  
 10      2.90 (m, 4H); Anal. Calcd. for  $\text{C}_{32}\text{H}_{25}\text{ClN}_4\text{O}_3$ : C, 70.01; H, 4.59; N, 10.20. Found:  
 C, 69.62; H, 4.44; N, 10.24.

[00147]      Example 260

1-[4-(benzyloxy)phenyl]-8-[[[(2-chloropyridin-3-yl)carbonyl]amino]-4,5-dihydro-  
 15      1H-benzo[g]indazole-3-carboxamide



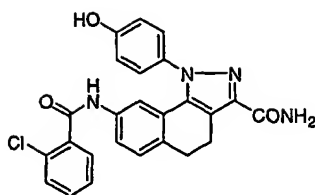
20      This compound was synthesized by following the same procedure as Example 259  
 except using 2-chloronicotinyl chloride in step 4;  $^1\text{H}$ NMR (DMSO, 400 MHz)  $\delta$ :  
 10.42 (s, 1H), 8.50 (d, 1H), 7.96 (d, 1H), 7.16-7.54 (m, 15H), 5.16 (s, 2H), 2.93 (m,  
 4H); Anal. Calcd. for  $\text{C}_{31}\text{H}_{24}\text{ClN}_5\text{O}_3$ : C, 67.70; H, 4.40; N, 12.73. Found: C, 66.75;  
 H, 4.17; N, 12.41.

25

[00148]      Example 261

8-[(2-chlorobenzoyl)amino]-1-(4-hydroxyphenyl)-4,5-dihydro-1H-  
 benzo[g]indazole-3-carboxamide

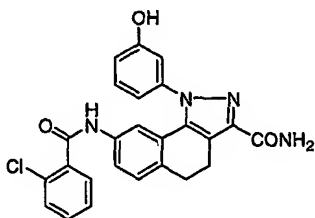




The final product from Example 259 (7.5 g, 0.014 mol) was dissolved of TFA (120 mL) and the dark brown solution was stirred at room temperature for 84 h. Solvent was removed and the residue was taken up with 200 mL of water. The solid was collected and air-dried to give 6.5 g of product as a pale white solid (83% yield); <sup>1</sup>HNMR (DMSO, 400 MHz) δ: 10.29 (s, 1H), 9.84 (s, 1H), 7.24-7.51 (m, 11 H), 6.87 (d, 2H), 2.90 (m, 4H); Anal. Calcd. for C<sub>25</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>3</sub> + 1.0 H<sub>2</sub>O: C, 62.96; H, 4.44; N, 11.75. Found: C, 62.92; H, 4.28; N, 11.76.

[00149] Example 262

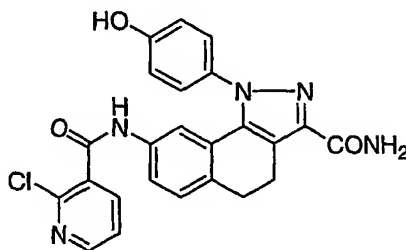
8-[(2-chlorobenzoyl)amino]-1-(3-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



This compound was synthesized by following the same procedure as Example 261 except using 3-benzyloxyphenylhydrazine hydrochloride in step 1; <sup>1</sup>HNMR (DMSO, 400 MHz) δ: 10.31 (s, 1H), 7.27-7.54 (m, 10H), 6.89 (m, 3H), 2.92 (m, 4H); Anal. Calcd. for C<sub>25</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>3</sub> + 0.5 H<sub>2</sub>O: C, 64.17; H, 4.31; N, 11.97. Found: C, 64.29; H, 4.36; N, 11.63.

[00150] Example 263

8-[[2-chloropyridin-3-yl]carbonyl]amino]-1-(4-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



5

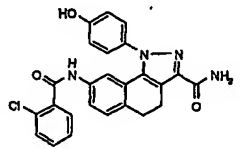
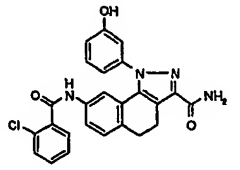
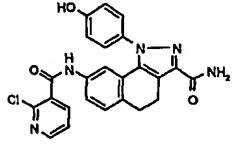
This compound was synthesized by following the same procedure as Example 261 except using 2-chloronicotinyl chloride in step 4;  $^1\text{H}$ NMR (DMSO, 400 MHz)  $\delta$ : 10.31 (s, 1H), 7.27-7.54 (m, 10H), 6.89 (m, 3H), 2.92 (m, 4H); Anal. Calcd. for  $\text{C}_{24}\text{H}_{18}\text{ClN}_5\text{O}_3$ : C, 62.68; H, 3.95; N, 15.23. Found: C, 62.03; H, 3.89; N, 14.83.

10

[00151] The bioactivity in the IKK2 resin assay of Examples 259-263 is shown Table 8.

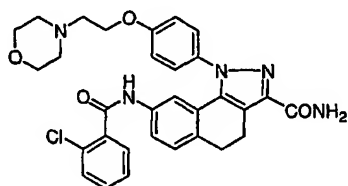
Table 8

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	549.03	1-[4-(benzyloxy)phenyl]-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	> 10 $\mu\text{M}$	550	259
	550.02	1-[4-(benzyloxy)phenyl]-8-[[2-chloropyridin-3-yl]carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10$ $\mu\text{M}$	551	260

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	458.91	8-[(2-chlorobenzoyl)amino]-1-(4-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	459	261
	458.90	8-[(2-chlorobenzoyl)amino]-1-(3-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	459	262
	459.89	8-[(2-chloropyridin-3-yl)carbonyl]amino]-1-(4-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	460	263

[00152] Example 264

8-[(2-chlorobenzoyl)amino]-1-[4-(2-morpholin-4-ylethoxy)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



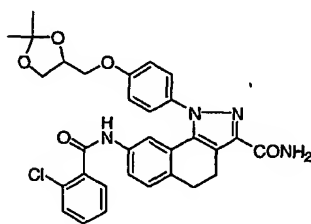
To a suspension of the product from Example 261 (0.6 g, 0.001 mol) and cesium carbonate in 10 mL of DMF was added 4-(2-chloroethyl)morpholine hydrochloride (0.19 g, 0.001 mol) in one portion. The reaction mixture was stirred at room temperature overnight. After the removal of solvent, the residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. This crude was purified by HPLC to

give 0.15 of product as a light yellow (26% yield);  $^1\text{H}$ NMR (DMSO, 400 MHz)  $\delta$ : 11.49 (brs, 1H), 10.33 (s, 1H), 7.14–7.54 (m, 10H), 4.53 (s, 2H), 3.82 (m, 2H), 3.58 (m, 8H), 3.08 (m, 2H), 2.93 (m, 4H); Anal. Calcd. for  $\text{C}_{31}\text{H}_{30}\text{ClN}_5\text{O}_4 \cdot 1.0 \text{ H}_2\text{O} \cdot 1.0 \text{ HCl}$ : C, 59.43; H, 5.31; N, 11.18. Found: C, 59.58; H, 5.26; N, 10.92.

5

**[00153]** Example 265

8-[(2-chlorobenzoyl)amino]-1-[4-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



10

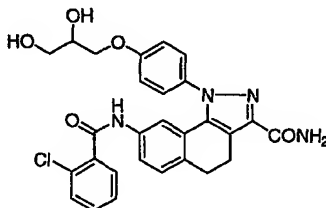
This compound was synthesized by following the same procedure as Example 264 except using 2,2-dimethyl-1,3-dioxolan-4-ylmethyl *p*-toluenesulfonate (78% yield);  $^1\text{H}$ NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 7.69 (d, 1H), 7.59 (m, 2H), 7.44 (d, 2H), 7.30–7.40 (m, 3H), 7.05 (d, 2H), 6.83 (d, 2H), 4.52 (m, 1H), 4.13 (m, 2H), 4.02 (m, 2H), 3.93 (m, 2H), 3.14 (m, 2H), 2.98 (m, 2H), 1.46 (s, 3H), 1.26 (s, 3H); Anal. Calcd. for  $\text{C}_{31}\text{H}_{29}\text{ClN}_4\text{O}_5$ : C, 64.98; H, 5.10; N, 9.78. Found: C, 64.56; H, 4.97; N, 9.68.

15

**[00154]** Example 266

8-[(2-chlorobenzoyl)amino]-1-[4-(2,3-dihydroxypropoxy)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

20



25

To a suspension of the product from Example 265(0.36 g, 0.00063 mol) in

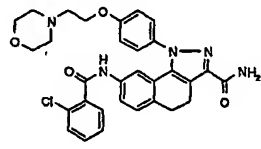
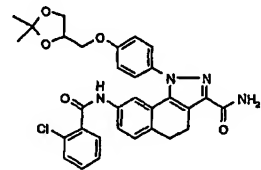
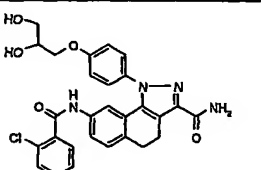
methanol was added 1N HCl and the mixture was heated at reflux for 16 h. Solvent was removed and the crude was recrystallized from water and methanol to give 0.24 g of the desired product as a white solid (72%); <sup>1</sup>H NMR (DMSO, 400 MHz) δ: 10.30 (s, 1H), 7.36-7.57 (m, 6H), 7.33 (d, 1H), 7.28 (brs, 1H), 7.18 (d, 1H), 7.09 (d, 2H), 4.98 (d, 1H), 4.68 (t, 1H), 4.10 (q, 1H), 4.05 (dd, 1H), 3.92 (dd, 1H), 3.83 (m, 5 2H), 3.45 (t, 1H), 3.16 (d, 2H), 2.94 (m, 4H); Anal. Calcd. for C<sub>28</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>5</sub>: C, 63.10; H, 4.73; N, 10.51. Found: C, 62.81; H, 4.45; N, 10.16.

**[00155]** The compounds of Examples 267–275 were synthesized as described in Example 264 using the appropriate aryl, substituted aryl, heteroaryl, substituted heteroaryl, substituted arylalkyl, substituted heteroarylalkyl, or cycloalkyl.

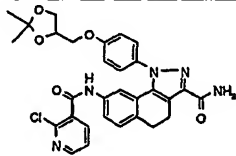
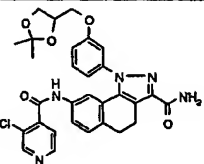
**[00156]** The bioactivity in the IKK2 Resin assay for the compounds of Examples 264-275 is shown in Table 9.

15

Table 9

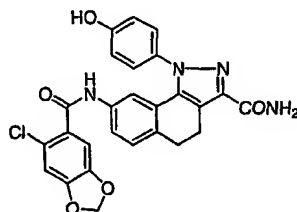
Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	572.07	8-[(2-chlorobenzoyl)amino]-1-[4-(2-morpholin-4-ylethoxy)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	573	264
	573.05	8-[(2-chlorobenzoyl)amino]-1-[4-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	574	265
	532.99	8-[(2-chlorobenzoyl)amino]-1-[4-(2,3-dihydroxypropoxy)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	533	266

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	533.98	8-[(3-chloroisonicotinoyl)amino]-1-[4-(2,3-dihydroxypropoxy)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	534	267
	611.08	8-[(2-chloro-4-(methylsulfonyl)benzoyl)amino]-1-[4-(2,3-dihydroxypropoxy)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	612	268
	548.00	8-[(5-amino-2-chlorobenzoyl)amino]-1-[4-(2,3-dihydroxypropoxy)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	548	269
	533.98	8-[(2-chloropyridin-3-yl)carbonyl]amino]-1-[4-(2,3-dihydroxypropoxy)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	534	270
	530.03	8-[(2-chlorobenzoyl)amino]-1-[4-{2-(dimethylamino)ethoxy}phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	530	271
	544.06	8-[(2-chlorobenzoyl)amino]-1-[4-{3-(dimethylamino)propoxy}phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	544	272
	651.14	8-[(2-chloro-4-(methylsulfonyl)benzoyl)amino]-1-[4-{(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy}phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	651	273

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	574.04	8-[(2-chloropyridin-3-yl)carbonylamino]-1-[4-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10$ $\mu\text{M}$	574	274
	574.04	8-[(3-chloroisonicotinoyl)amino]-1-[3-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10$ $\mu\text{M}$	574	275

**[00157]** Example 276

8-[(2-chlorobenzoyl)amino]-1-(4-cyanophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



- 10 **[00158]** Step 1: The product (45.0 g, 0.096 mol) from step 1 of Example 261 was hydrogenated in 400 mL of acetic acid with  $\text{Pd}(\text{OH})_2/\text{C}$  as catalyst for 17 h under 15 psi in a Parr shaker. After the removal of solvent, the residue was triturated with a mixture of methanol and ether (1:2) to give 23.0 g of the desired product as a white solid (68% yield);  $^1\text{H}$ NMR (DMSO, 400 MHz)  $\delta$ : 10.06 (s, 1H),
- 15 7.27 (d, 2H), 6.98 (d, 1H), 6.92 (d, 2H), 6.43 (dd, 1H), 6.02 (d, 1H), 4.82 (brs, 2H), 4.29 (q, 2H), 2.75 (m, 2H), 1.30 (t, 3H).

**[00159]** Step 2: A sealed reaction vessel containing the product from step 1 (25.0 g, 0.072 mol) and 40 mL of liquid ammonia in 250 mL of absolute alcohol

was heated at 120°C and 600 psi for 30 h. After cooling, the precipitate was collected by filtration to give 16.7 g of product as a pale yellow solid (73% yield); <sup>1</sup>HNMR (CDCl<sub>3</sub>, 400 MHz) δ: 7.44 (s, 1H), 7.27 (d, 2H), 7.20 (s, 1H), 6.97 (d, 1H), 6.91 (d, 2H), 6.40 (d, 1H), 6.03 (s, 1H), 4.77 (brs, 2H), 2.85 (m, 2H), 2.72 (m, 2H).

5

[00160] Step 3: To a solution of the product from step 1 (5.25 g, 0.016 mol) and TBDMSCl (3.0 g, 0.02 mol) in 100 mL of DMF was added imidazole (2.72 g, 0.04 mol) in one portion. The reaction mixture was stirred at room temperature for 36 h. Solvent was removed and the residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. This crude was purified by chromatography on silica gel (ethyl acetate/hexane, 1:1) to give 4.0 g of product as a white solid (57% yield). The NMR was consistent with the proposed structure.

10

15 [00161] Step 4: To a mixture of the product from step 3 (1.05 g, 0.0024 mol) and 2-chloro-4,5-methylenedioxanylbenzoic acid (0.73 g, 0.0036 mol) in 25 mL of DMF was added 1 mL of diisopropylethylamine, followed by the addition of HATU (1.37 g, 0.0036 mol). The reaction was stirred at room temperature for 16 h and concentrated. The residue was partitioned between water and ethyl acetate and the organic phase was concentrated. This crude was then dissolved in 20 mL of THF and treated with 10 eq of TBAF for 1 h at RT. After the removal of solvent, the residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and triturated with a mixture of acetonitrile to give 1.04 g of desired product as an off-white solid (86% yield); <sup>1</sup>HNMR (DMSO, 400 MHz) δ: 10.17 (s, 1H), 9.85 (s, 1H), 7.47 (m, 2H), 7.27 (m, 5H), 7.14 (s, 1H), 7.04 (s, 1H), 6.88 (d, 2H), 6.12 (s, 2H), 2.92 (m, 4H).

20

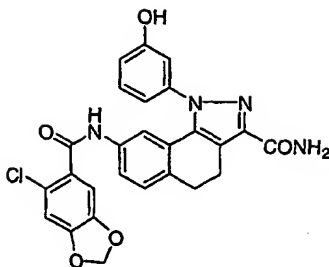
25

[00162] Example 277

30

8-{[(6-chloro-1,3-benzodioxol-5-yl)carbonyl]amino}-1-(3-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

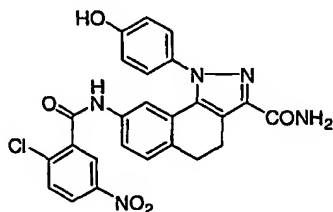




This compound was synthesized by following the same procedure as Example 276 except using 3-benzyloxymethylphenylhydrazine hydrochloride in step 1; <sup>1</sup>HNMR (DMSO, 400 MHz)  $\delta$ : 10.19 (s, 1H), 9.86 (s, 1H), 7.51 (m, 2H), 7.31 (m, 3H), 7.24 (d, 1H), 7.14 (s, 1H), 7.04 (s, 1H), 6.88 (m, 3H), 6.12 (s, 2 H), 2.91 (m, 4H); Anal. Calcd. for C<sub>26</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>5</sub>: C, 62.10; H, 3.81; N, 11.14. Found: C, 61.52; H, 3.53; N, 11.11.

[00163] Example 278

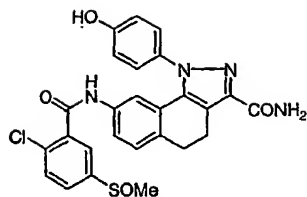
8-[(2-chloro-5-nitrobenzoyl)amino]-1-(4-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



This compound was synthesized by following the same procedure as Example 276 except using 2-chloro-5-nitrobenzoic acid in step 4; Anal. Calcd. for C<sub>25</sub>H<sub>18</sub>ClN<sub>5</sub>O<sub>5</sub>·1.5 H<sub>2</sub>O: C, 56.56; H, 3.99; N, 13.19. Found: C, 56.89; H, 4.45; N, 12.81.

[00164] Example 279

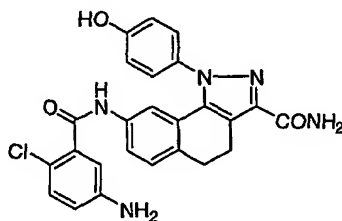
8-[[2-chloro-5-(methylsulfinyl)benzoyl]amino]-1-(4-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



This compound was synthesized by following the same procedure as Example 276 except using 2-chloro-5-(methylthio)benzoic acid in step 4 and then oxidized to the  
 5 desired product with *m*CPBA; <sup>1</sup>HNMR (DMSO, 400 MHz)  $\delta$ : 10.43 (s, 1H), 9.85 (s, 1H), 7.26-7.79 (m, 10H), 6.88 (d, *J* = 8.5 Hz, 2H), 2.92 (m, 4H), 2.80 (s, 3H); Anal. Calcd. for C<sub>26</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>4</sub>S: C, 59.94; H, 4.06; N, 10.75; S, 6.15. Found: C, 59.48; H, 4.09; N, 10.54; S, 6.18.

10 [00165] Example 280

8-[(5-amino-2-chlorobenzoyl)amino]-1-(4-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



15

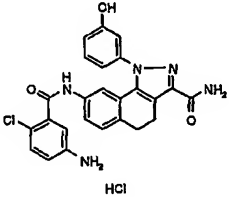
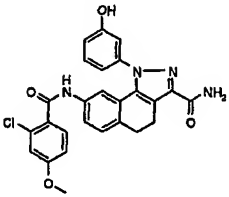
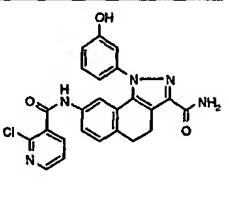
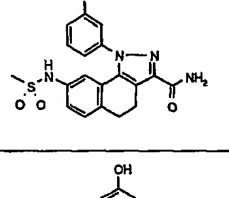
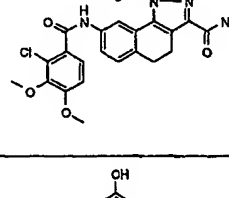
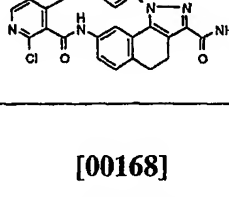
This compound was synthesized by following the same procedure as Example 276 except using 5-[(*tert*-butoxycarbonyl)amino]-2-chlorobenzoic acid in step 4 and then deprotected with 4N HCl in dioxane; <sup>1</sup>HNMR (DMSO, 400 MHz)  $\delta$ : 10.19 (s, 1H), 9.84 (s, 1H), 7.49 (d, 1H), 7.46 (d, 1H), 7.28-7.31 (m, 5H), 7.12 (d, 1H), 6.88  
 20 (d, 2H), 6.64 (m, 2H), 2.90 (m, 4H), 2.80; Anal. Calcd. for C<sub>25</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>3</sub>·3.0 H<sub>2</sub>O: C, 56.87; H, 4.96; N, 13.26. Found: C, 56.18; H, 5.10; N, 13.09.

[00166] The compounds of Examples 281-287 listed in the Table 10 were prepared according to the procedure of Example 276 using the appropriate acylating  
 25 agent.

[00167] The bioactivity in the IKK2 Resin assay for the compounds of Examples 276-287 is shown in Table10.

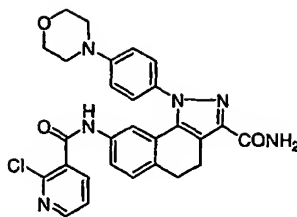
Table 10

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	502.91	8-[[[(6-chloro-1,3-benzodioxol-5-yl)carbonyl]amino]-1-(4-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	503	276
	502.92	8-[[[(6-chloro-1,3-benzodioxol-5-yl)carbonyl]amino]-1-(3-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	503	277
	503.91	8-[(2-chloro-5-nitrobenzoyl)amino]-1-(4-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	504	278
	521.00	8-[(2-chloro-5-(methylsulfinyl)benzoyl)amino]-1-(4-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	521	279
	473.92	8-[(5-amino-2-chlorobenzoyl)amino]-1-(4-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	474	280
	459.90	8-[(3-chloroisonicotinoyl)amino]-1-(3-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	460	281

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	510.38	8-[(5-amino-2-chlorobenzoyl)amino]-1-(3-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$\leq 1 \mu\text{M}$	511	282
	488.94	8-[(2-chloro-4-methoxybenzoyl)amino]-1-(3-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	489	283
	459.90	8-[[2-(2-chloropyridin-3-yl)carbonyl]amino]-1-(3-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	460	284
	398.44	1-(3-hydroxyphenyl)-8-[(methylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	399	285
	518.96	8-[(2-chloro-3,4-dimethoxybenzoyl)amino]-1-(3-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	519	286
	473.92	8-[[2-(2-chloro-4-methylpyridin-3-yl)carbonyl]amino]-1-(3-hydroxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	474	287

## [00168] Example 288

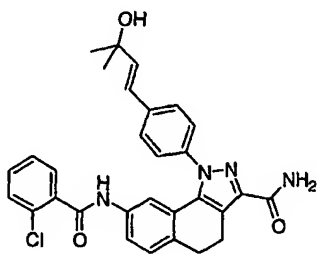
8-[[2-(2-chloropyridin-3-yl)carbonyl]amino]-1-(4-morpholin-4-ylphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



This compound was synthesized in an analogous manner to Example 3 by substituting 4-morpholinylphenylhydrazine hydrochloride and 2-chloronicotinyl chloride.; <sup>1</sup>HNMR (DMSO, 400 MHz)  $\delta$ : 10.39 (s, 1H), 8.50 (d, 1H), 7.94 (d, 1H), 7.05-7.53 (m, 10H), 3.74 (m, 4H), 3.18 (m, 4H), 2.92 (m, 4H); Anal. Calcd. for C<sub>28</sub>H<sub>25</sub>ClN<sub>6</sub>O<sub>3</sub>: C, 63.57; H, 4.76; N, 15.89. Found: C, 63.19; H, 4.61; N, 15.48. IKK-2 resin IC<sub>50</sub>  $\leq$ 10  $\mu$ M.

[00169] Example 289

8-[(2-chlorobenzoyl)amino]-1-{4-[(1E)-3-hydroxy-3-methylbut-1-enyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



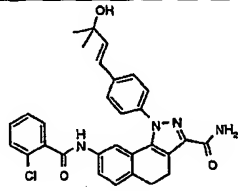
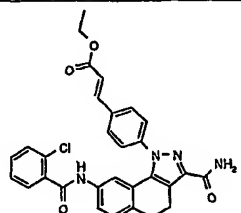
A 50 mL round bottomed flask with a magnetic stir bar was charged with 1-(4-bromophenyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (987 mg, 1.89 mmol), palladium (II) acetate (44 mg, 0.19 mmol), 1,1'-biphenyl-2-yl[di(tert-butyl)]phosphine (254 mg, 0.822 mmol), and dimethylformamide (20 mL). The resulting solution was sparged with argon for 10 minutes. To the solution was added 2-methyl-3-buten-2-ol (823 mg, 6.07 mmol) and triethylamine (614 mg, 6.07 mmol). The solution was sparged with argon for an additional 2 minutes. The flask was sealed with a rubber septum and heated to

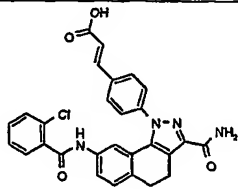
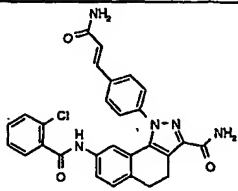
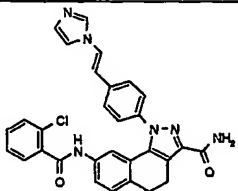
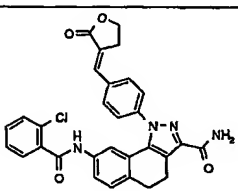
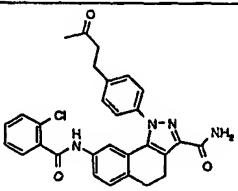
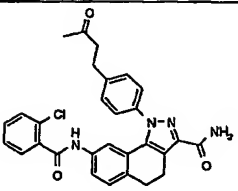
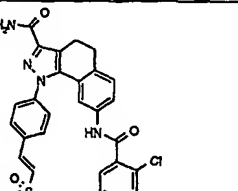
100 °C in an oil bath for 90 minutes. The reaction was allowed to cool to room temperature and water was added. The resulting precipitate was collected and purified by silica gel chromatography (100% hexane to 100% ethyl acetate). The pure fractions were combined, concentrated to dryness, triturated with diethyl ether, and dried under vacuum to give 215 mg of 8-[(2-chlorobenzoyl)amino]-1-{4-[(1E)-3-hydroxy-3-methylbut-1-enyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (0.408 mmol, 21% yield) as a solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.29 (s, 6 H), 2.88-2.98 (m, 4 H), 4.76 (s, 1 H), 6.48 (d, 1 H), 6.58 (d, 1 H), 7.23 (d, 1 H), 7.30-7.50 (m, 8 H), 7.53-7.59 (m, 3 H), 10.28 (s, 1 H); MS (ESI+) for C<sub>30</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>3</sub> *m/z* 527 (M+H)<sup>+</sup>.

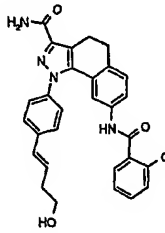
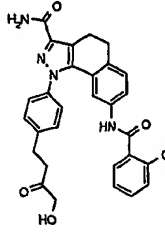
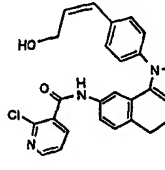
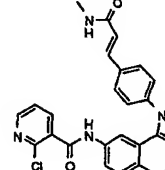
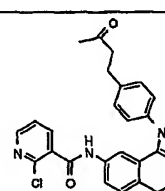
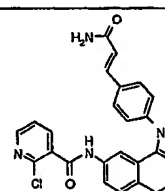
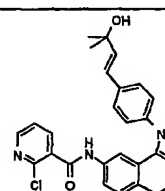
[00170] The compounds of Example 290-308 listed in the Table 11 were prepared according to the procedure of Example 289 using the appropriate alkene.

[00171] The bioactivity in the IKK2 Resin assay for the compounds of Examples 289-308 is shown in Table 11.

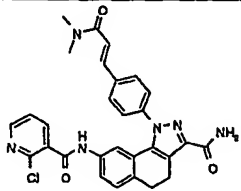
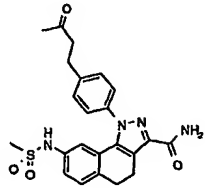
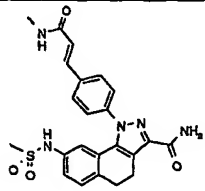
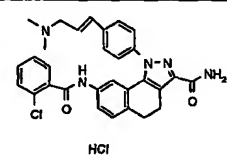
Table 11

Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	527.03	8-[(2-chlorobenzoyl)amino]-1-{4-[(1E)-3-hydroxy-3-methylbut-1-enyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	527	289
	541.01	ethyl (2E)-3-(4-{3-(aminocarbonyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazol-1-yl}phenyl)prop-2-enoate	1 ≤ 10 μM	541	290

Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	512.96	(2E)-3-(4-(3-(aminocarbonyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazol-1-yl)phenyl)prop-2-enoic acid	$\leq 1 \mu\text{M}$	513	291
	511.97	1-{4-[(1E)-3-amino-3-oxoprop-1-enyl]phenyl}-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	512	292
	535.01	8-[(2-chlorobenzoyl)amino]-1-{4-[(E)-2-(1H-imidazol-1-yl)ethenyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	535	293
	539.00	8-[(2-chlorobenzoyl)amino]-1-{4-[(E)-2-(2-oxodihydrofuran-3(2H)-ylidene)methyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	539	294
	513.00	8-[(2-chlorobenzoyl)amino]-1-{4-[(1E)-3-hydroxybut-1-enyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	513	295
	513.00	8-[(2-chlorobenzoyl)amino]-1-[4-(3-oxobutyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	513	296
	547.04	8-[(2-chlorobenzoyl)amino]-1-{4-[(E)-2-(methylsulfonyl)ethenyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	547	297

Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	513.00	8-[(2-chlorobenzoyl)amino]-1-{4-[(1E)-4-hydroxybut-1-enyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	513	298
	529.00	8-[(2-chlorobenzoyl)amino]-1-[4-(4-hydroxy-3-oxobutyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	529	299
	499.96	8-[[2-(2-chloropyridin-3-yl)carbonyl]amino]-1-{4-[(1Z)-3-hydroxyprop-1-enyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	500	300
	526.99	8-[[2-(2-chloropyridin-3-yl)carbonyl]amino]-1-{4-[(1E)-3-(methylamino)-3-oxoprop-1-enyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	527	301
	513.99	8-[[2-(2-chloropyridin-3-yl)carbonyl]amino]-1-[4-(3-oxobutyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	514	302
	512.96	1-[4-[(1E)-3-amino-3-oxoprop-1-enyl]phenyl]-8-[[2-(2-chloropyridin-3-yl)carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	513	303
	528.01	8-[[2-(2-chloropyridin-3-yl)carbonyl]amino]-1-{4-[(1E)-3-hydroxy-3-methylbut-1-enyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	528	304

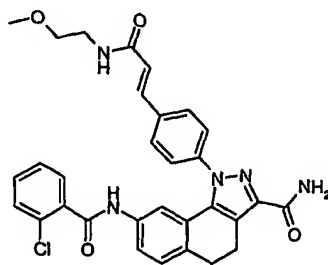


Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	541.01	8-([(2-chloropyridin-3-yl)carbonyl]amino)-1-[4-[(1E)-3-(dimethylamino)-3-oxoprop-1-enyl]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	541	305
	452.54	8-[(methylsulfonyl)amino]-1-[4-(3-oxobutyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	453	306
	465.54	1-[4-[(1E)-3-(methylamino)-3-oxoprop-1-enyl]phenyl]-8-[(methylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	566	307
 HCl	562.50	8-([(2-chlorobenzoyl)amino]-1-[4-[(1E)-3-(dimethylamino)prop-1-enyl]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$1 \leq 10 \mu\text{M}$	526	308

## [00172] Example 309

8-[(2-chlorobenzoyl)amino]-1-[4-[(1E)-3-[(2-methoxyethyl)amino]-3-oxoprop-1-enyl]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

5



To a 50 mL syringe barrel equipped with a fritted disk was added 2.02 g of PS-MB-CHO (Argonaut Technologies, 1.46 mmol/g loading). The resin was washed with N,N-dimethylformamide. To the resin was added a solution of sodium

10

5 triacetoxyborohydride (3.20 g, 15.1 mmol) dissolved in trimethylorthoformate (1.5 mL), acetic acid (1.5 mL), and N,N-dimethylformamide (12 mL). 2-Methoxyethylamine (1.11 g, 14.8 mmol) was added to the mixture. The mixture was allowed to shake on an orbital shaker for 16 hrs. The solution was drained from the resin and washed with a solution of 8 parts N,N-dimethylformamide to 1 part trimethylorthoformate to 1 part acetic acid. The resin was then washed with N,N-dimethylformamide, 1 part N,N-dimethylformamide to 1 part triethylamine, N,N-dimethylformamide, dichloromethane, and diethyl ether. The resin was dried under vacuum.

10

[00173] To a 4 mL peptide flask was added 100mg of the resin. A solution of HBTU (127 mg, 0.336 mmol), 1-hydroxybenzotriazole (52 mg, 0.38 mmol), triethylamine (34 mg, 0.34 mmol), and (2E)-3-(4-{3-(aminocarbonyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazol-1-yl}phenyl)prop-2-enoic acid (172 mg, 0.335 mmol) in 2mL of N,N-dimethylformamide was added to the resin. The peptide flask was agitated on an orbital shaker for 16 hrs, after which the solution was drained and the resin was washed with DMF, dichloromethane, and diethyl ether. The resin was dried under vacuum.

15

20 [00174] The resin was suspended in 2 mL of 90% aqueous trifluoroacetic acid and agitated for 30 minutes. The solution was filtered. The resin was washed with 2 mL of 90% aqueous trifluoroacetic acid, with the wash being collected. The TFA solutions were combined, diluted to 15 mL with water, and concentrated to dryness. The resulting oil was triturated with methanol to yield the title compound.

25 MS (ESI+) for  $C_{31}H_{28}ClN_5O_4$   $m/z$  570.2 (M+H)<sup>+</sup>.

[00175] The compounds of Examples 310-315 listed in the Table 12 were prepared according to the procedure of Example 309 using the appropriate amine.

30

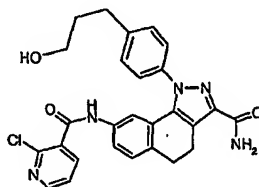
[00176] The bioactivity in the IKK2 Resin assay for the compounds of Examples 309-315 is shown in Table 12.

Table 12

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	570.0	8-[(2-chlorobenzoyl)amino]-1-(4-[(1E)-3-[(2-methoxyethyl)amino]-3-oxoprop-1-enyl]phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	570	309
	592.1	8-[(2-chlorobenzoyl)amino]-1-(4-[(1E)-3-[(2-furylmethyl)amino]-3-oxoprop-1-enyl]phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	592	310
	526.0	8-[(2-chlorobenzoyl)amino]-1-(4-[(1E)-3-(methylamino)-3-oxoprop-1-enyl]phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	526	311
	540.0	8-[(2-chlorobenzoyl)amino]-1-(4-[(1E)-3-(ethylamino)-3-oxoprop-1-enyl]phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	540	312
	602.1	1-(4-[(1E)-3-(benzylamino)-3-oxoprop-1-enyl]phenyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	602	313
	387.44	8-amino-1-(4-[(1E)-3-(methylamino)-3-oxoprop-1-enyl]phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	388	314
	479.56	1-(4-[(1E)-3-(dimethylamino)-3-oxoprop-1-enyl]phenyl)-8-[(methylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	480	315

**[00177]** Example 316

8-[[2-chloropyridin-3-yl]carbonyl]amino}-1-[4-(3-hydroxypropyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



5

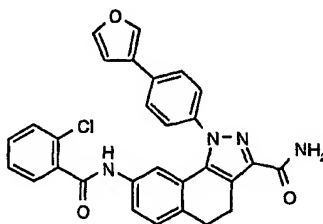
Using standard hydrogenation conditions 8-[[2-chloropyridin-3-yl]carbonyl]amino}-1-[4-[(1Z)-3-hydroxyprop-1-enyl]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide was converted to 8-[[2-chloropyridin-3-yl]carbonyl]amino}-1-[4-(3-hydroxypropyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide. MS (ESI+) for  $m/z$  502 ( $M+H$ )<sup>+</sup>. IKK-2 resin  $IC_{50} \leq 1 \mu M$ .

10

**[00178]** Example 317

8-[(2-chlorobenzoyl)amino]-1-[4-(3-furyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

15



**[00179]** Step 1: A suspension of ethyl 1-(4-bromophenyl)-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxylate (4.4 g) in THF (80 mL) was treated with 1 N aq. NaOH (80 mL) and stirred vigorously overnight. The reaction mixture was diluted with ethyl acetate and acidified to pH = 2 with 1 N aq. HCl. The organic layer was separated and the aqueous fraction extracted with EtOAc (3x).

20

Combined extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo to afford 4.0 g (97%) of 1-(4-bromophenyl)-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxylic acid as a solid: MS(ESI+) 414  $[\text{M}+\text{H}]^+$ .  $^1\text{H}$  NMR (400 MHz,  $\text{d}^6$  DMSO)  $\delta$  8.07 (dd, 1H), 7.83 (d, 2H), 7.66 (d, 1H), 7.56 (d, 2H), 7.42 (d, 1H), 3.10 (m, 2H), 2.99 (m, 2H).

[00180] Step 2: A suspension of Rink amide resin (5.3g, 2.5 mmol, 0.47 meq/g, NovaBiochem), in 30 % piperidine/DMF was prepared in a solid phase reactor equipped with an overhead stirrer. The mixture was stirred for 15 min, filtered, and treated a second time with 30 % piperidine/DMF for 15 min. The solvent was removed by filtration and the resin washed with DMF (3x), MeOH (3x), and DCM (4x). A solution of 1-(4-bromophenyl)-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxylic acid (2.07 g) in 1:1 DCM/DMF (10 mL) was prepared and added to the resin, followed by 1M HOBt in DMF (5 mL) and 1M DIC in DMF (5 mL). The resin was stirred at RT. After stirring for 16 h, the resin was washed with DMF (3x), MeOH (3x), DCM (4x), and filter to afford loaded resin. Resin loading was determined by direct cleavage  $^1\text{H}$  NMR: 0.569 mmol/g. Evaporated direct cleavage NMR sample from the resin gave an oil: MS(ESI+) 413  $[\text{M}+\text{H}]^+$ .  $^1\text{H}$  NMR (400 MHz, 10%TFA/ $\text{CDCl}_3$ ):  $\delta$  8.10 (dd, 1H), 7.76 (d, 2H), 7.63 (d, 1H), 7.53 (d, 1H), 7.41 (d, 2H), 3.16 (m, 4H).

[00181] Step 3: In a solid phase reactor equipped with an overhead stirrer to a suspension of resin from step 2 (7.8 g, 4.43 mmol) in NMP (15 mL) was added 2M  $\text{SnCl}_2$  in NMP (15 mL). The mixture was stirred for 1 h, filtered, and retreated with 2M  $\text{SnCl}_2$  in NMP (15 mL). After stirring overnight the resin was filtered, washed with DMF (3x), MeOH (3x), DCM (4x), filtered, and air dried to afford the intermediate amine resin. Determined resin loading by direct cleavage  $^1\text{H}$  NMR: 0.414 mmol/g. In a solid phase reactor equipped with an overhead stirrer was prepared a suspension of 0.4 g of the amine resin in NMP.

30

[00182] Step 4: The resin was allowed to stir for 5 min and subsequently treated with a solution of 2-chlorobenzoic acid (126 mg) in NMP (1 mL). The

mixture was treated with HATU (307 mg), DIEA (0.28 mL) and stirred for 1h. The resultant resin was filtered, subjected to a second treatment of 2-chlorobenzoic acid, HATU and DIEA in NMP, and allowed to stir. After stirring overnight, the resin was filtered, washed with DMF (3x), MeOH (3x), and DCM (4x). The resin was  
5 filtered and air dried to afford resin. Determined resin loading by direct cleavage <sup>1</sup>H NMR: 0.702 mmol/g.

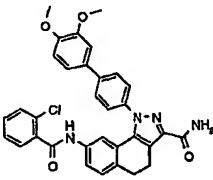
[00183] Step 5: To a reaction vessel was added resin from step 4 (0.20g, 0.09 mmol) in a suspension of toluene/EtOH (2:1). The vessels were purged with  
10 argon for 5 min and subsequently treated with Pd(PPh<sub>3</sub>)<sub>4</sub> (41.6 mg, 0.036mmol), an 3-furylboronic acid (0.2mmol), and 2M Na<sub>2</sub>CO<sub>3</sub> (200μL, 0.4mmol). The vessels were heated to 100°C and allowed to agitate for 30 h. Each vessel was quenched with 25% NH<sub>4</sub>OH for 30min, filtered and washed three times each with DMF, MeOH, MeOH:H<sub>2</sub>O (1:1), 0.2N HCl, MeOH:H<sub>2</sub>O (1:1), MeOH and DCM. The  
15 resins were allowed to dry and cleaved with 10% TFA/DCM (2 mL) for 30 min. The resins were washed twice with 0.5 mL DCM and the combined filtrates concentrated to afford the desired final product.

[00184] The compounds of Examples 318-323 listed in the Table 13 were  
20 prepared according to the procedure of Example 317 using the appropriate boronic acid in step 5.

[00185] The bioactivity in the IKK2 Resin assay for the compounds of Examples 316-323 is shown in Table 13.

Table 13

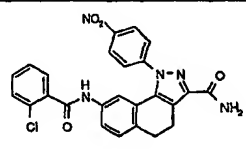
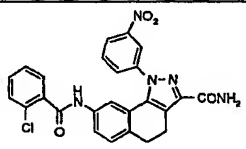
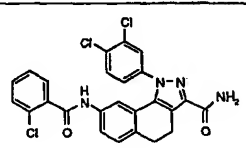
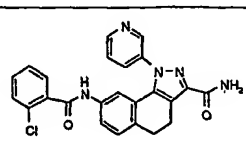
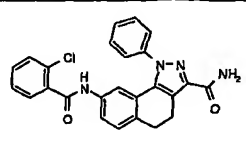
Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	501.96	8-[(2-chloropyridin-3-yl)carbonyl]amino]-1-[4-(3-hydroxypropyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	502	316
	508.97	8-[(2-chlorobenzoyl)amino]-1-[4-(3-furyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	509	317
	520.00	8-[(2-chlorobenzoyl)amino]-1-[4-(pyridin-3-yl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	520	318
	549.03	8-[(2-chlorobenzoyl)amino]-1-[3'-(hydroxymethyl)-1,1'-biphenyl-4-yl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	549	319
	534.02	1-(3'-amino-1,1'-biphenyl-4-yl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	534	320
	563.02	4'-[3-(aminocarbonyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazol-1-yl]-1,1'-biphenyl-3-carboxylic acid	$1 \leq 10 \mu\text{M}$	563	321
	563.02	4'-[3-(aminocarbonyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazol-1-yl]-1,1'-biphenyl-4-carboxylic acid	$1 \leq 10 \mu\text{M}$	563	322

Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	579.06	8-[(2-chlorobenzoyl)amino]-1-(3',4'-dimethoxy-1,1'-biphenyl-4-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	579	323

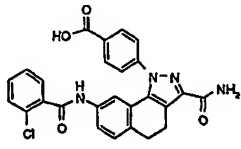
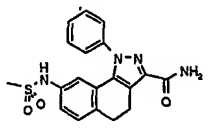
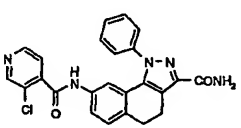
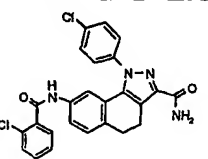
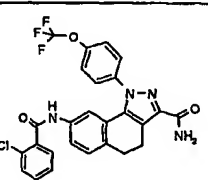
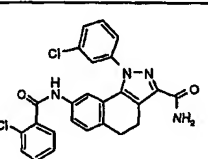
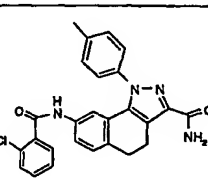
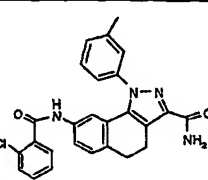
[00186] The compounds of Examples 324-366 in Table 14 were prepared in a manner analogous to Example 3 using the appropriate hydrazine and acylating or

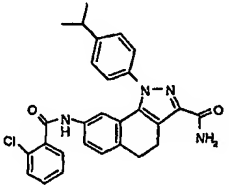
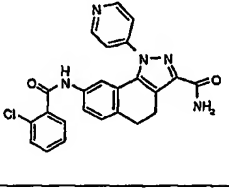
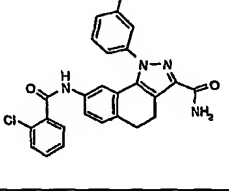
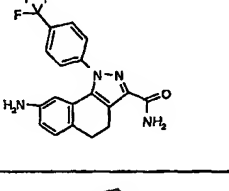
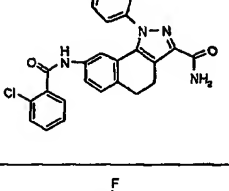
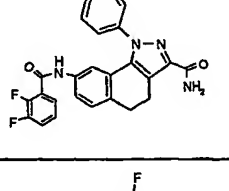
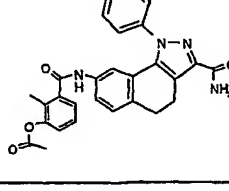
5 sulfonating agent. The bioactivity in the IKK2 Resin assay for the compounds of Examples 324-366 is shown in Table 14.

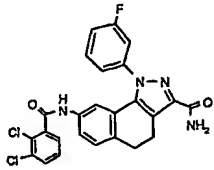
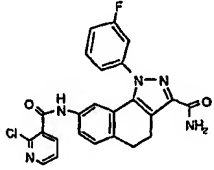
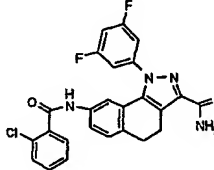
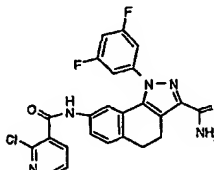
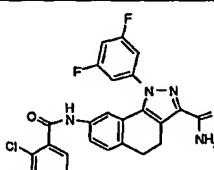
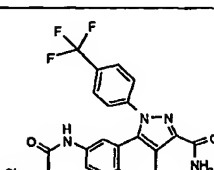
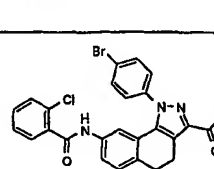
Table 14

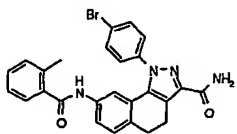
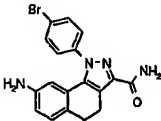
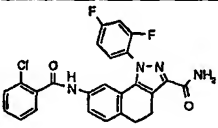
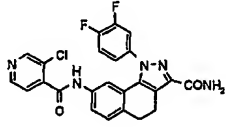
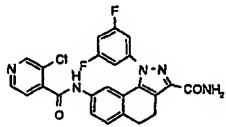
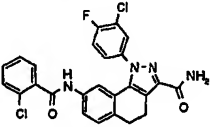
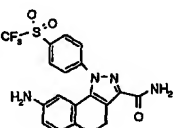
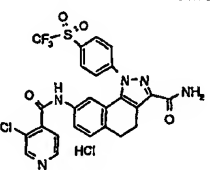
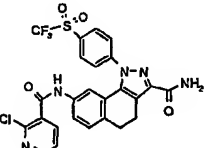
Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	487.91	8-[(2-chlorobenzoyl)amino]-1-(4-nitrophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	488	324
	487.91	8-[(2-chlorobenzoyl)amino]-1-(3-nitrophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	488	325
	511.80	8-[(2-chlorobenzoyl)amino]-1-(3,4-dichlorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	512	326
	443.90	8-[(2-chlorobenzoyl)amino]-1-pyridin-3-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	444	327
	442.91	8-[(2-chlorobenzoyl)amino]-1-phenyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	443	328

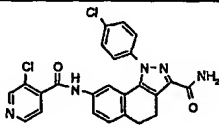
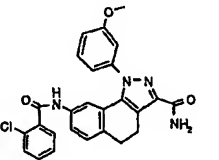
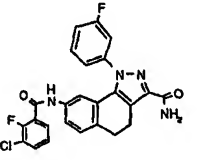
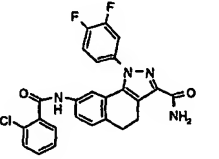
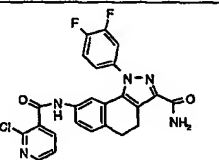
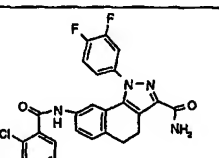
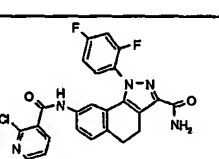


Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	486.92	4-[(3-(aminocarbonyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazol-1-yl)benzoic acid	$1 \leq 10 \mu\text{M}$	487	329
	382.44	8-[(methylsulfonyl)amino]-1-phenyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	383	330
	443.90	8-[(3-chloroisonicotinoyl)amino]-1-phenyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	444	331
	477.35	8-[(2-chlorobenzoyl)amino]-1-(4-chlorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	478	332
	526.91	8-[(2-chlorobenzoyl)amino]-1-[4-(trifluoromethoxy)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	527	333
	477.35	8-[(2-chlorobenzoyl)amino]-1-(3-chlorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	478	334
	456.94	8-[(2-chlorobenzoyl)amino]-1-(4-methylphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	457	335
	456.94	8-[(2-chlorobenzoyl)amino]-1-(3-methylphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	457	3336

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	484.99	8-[(2-chlorobenzoyl)amino]-1-(4-isopropylphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10$ $\mu\text{M}$	485	337
	443.89	8-[(2-chlorobenzoyl)amino]-1-pyridin-4-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1$ $\mu\text{M}$	444	338
	460.89	8-[(2-chlorobenzoyl)amino]-1-(3-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1$ $\mu\text{M}$	461	339
	372.35	8-amino-1-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10$ $\mu\text{M}$	373	340
	460.89	8-[(2-chlorobenzoyl)amino]-1-(2-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1$ $\mu\text{M}$	461	341
	462.43	8-[(2,3-difluorobenzoyl)amino]-1-(3-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10$ $\mu\text{M}$	463	342
	498.51	3-({[3-(aminocarbonyl)-1-(3-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazol-8-yl]amino}carbonyl)-2-methylphenyl acetate	$1 \leq 10$ $\mu\text{M}$	499	343

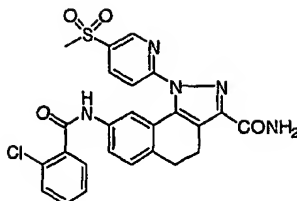
Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	495.34	8-[(2,3-dichlorobenzoyl)amino]-1-(3-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	496	344
	461.88	8-[(2-chloropyridin-3-yl)carbonyl]amino-1-(3-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	462	345
	478.88	8-[(2-chlorobenzoyl)amino]-1-(3,5-difluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	479	346
	479.87	8-[(2-chloropyridin-3-yl)carbonyl]amino-1-(3,5-difluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	480	347
	513.33	8-[(2,3-dichlorobenzoyl)amino]-1-(3,5-difluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	513	348
	510.91	8-[(2-chlorobenzoyl)amino]-1-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	511	349
	521.81	1-(4-bromophenyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	521	350

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	501.39	1-(4-bromophenyl)-8-[(2-methylbenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	502	351
	383.25	8-amino-1-(4-bromophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	383	352
	478.89	8-[(2-chlorobenzoyl)amino]-1-(2,4-difluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	479	353
	479.87	8-[(3-chloroisonicotinoyl)amino]-1-(3,4-difluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	480	354
	479.87	8-[(3-chloroisonicotinoyl)amino]-1-(3,5-difluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	480	355
	495.34	8-[(2-chlorobenzoyl)amino]-1-(3-chloro-4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	495	356
	436.42	8-amino-1-{4-[(trifluoromethyl)sulfonyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	437	357
	612.42	8-[(3-chloroisonicotinoyl)amino]-1-{4-[(trifluoromethyl)sulfonyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$\leq 1 \mu\text{M}$	576	358
	575.96	8-[(2-chloropyridin-3-yl)carbonyl]amino-1-{4-[(trifluoromethyl)sulfonyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	576	359

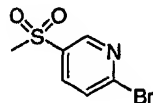
Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	478.34	1-((4-chlorophenyl)carbonyl)amino)-8-((4-chloropyridin-3-yl)carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	478	360
	472.94	8-((2-chlorobenzoyl)amino)-1-(3-methoxyphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	473	361
	478.88	8-((3-chloro-2-fluorobenzoyl)amino)-1-(3-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	479	362
	478.88	8-((2-chlorobenzoyl)amino)-1-(3,4-difluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	479	363
	479.87	8-((2-chloropyridin-3-yl)carbonyl)amino)-1-(3,4-difluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	480	364
	513.33	8-((2,3-dichlorobenzoyl)amino)-1-(3,4-difluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	513	365
	479.88	8-((2-chloropyridin-3-yl)carbonyl)amino)-1-(2,4-difluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	480	366

## [00187] Example 367

8-((2-chlorobenzoyl)amino)-1-[5-(methylsulfonyl)pyridin-2-yl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

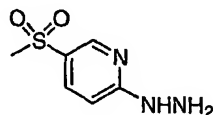


[00188] Step 1

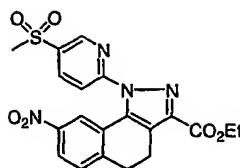


5 To a suspension of 2,5-dibromopyridine (12.0 g, 0.05 mol) in ether was added <sup>n</sup>BuLi (32 mL of 1.6 N in hexane, 0.05 mol) at -78°C dropwise. The purple suspension was stirred for 1 hour and then treated with dimethyl disulfide. The reaction mixture was kept at this temperature for 1 h and ½ h at 0°C. The reaction was quenched with a mixture of concentrated HCl and ether. The organic phase  
10 was washed with brine, dried over MgSO<sub>4</sub>, and filtered. The filtrate was concentrated to give 10.3 g of crude as brown oil, which was used without purification. To a solution of this crude (10.0 g, 0.05 mol) in methanol (200 mL) was added a solution of OXONE<sup>®</sup> in 300 mL of water. The reaction was stirred at room temperature for 72 h. Solvent was removed and the residue was basified with  
15 50% NaOH solution. The precipitate was collected by filtration, air-dried to give 8.2 g of product as a white crystal (72% yield over two step). NMR spectrum was consistent with the proposed structure.

[00189] Step 2

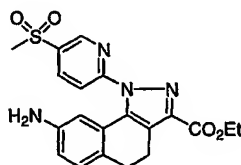


20 A mixture of the product from step 1 (8.0 g, 0.034 mol) and hydrazine (2.3 g, 0.068 mol) in 100 mL of ethanol was heated at reflux for 2 h. cooled to room temperature, and the solid was collected by filtration, washed with sat. NaHCO<sub>3</sub>, water, air-dried  
25 to give 4.0 g of crude as a pale white solid (63% yield); NMR spectrum was consistent with the proposed structure.

**[00190]**      Step 3

5      A mixture of the product from step 2 (1.4 g, 0.007 mol) and ethyl (7-nitro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)(oxo)acetate (2.03 g, 0.007 mol) in 75 mL of acetic acid was heated at reflux under nitrogen for 3 h. The solvent was removed and the residue was treated with a mixture of methanol/ethyl acetate/ether to give 1.67 g of the product as a yellow solid (54% yield); <sup>1</sup>HNMR (DMSO, 400 MHz) δ:

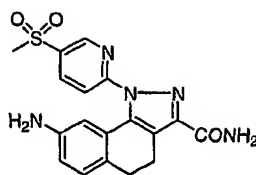
10      8.98 (dd, 1H), 8.68 (dd, 1H), 8.21 (d, 1H), 8.13 (dd, 1H), 7.95 (d, 1H), 7.68 (d, 1H), 4.37 (q, 2H), 3.42 (s, 3H), 3.11 (m, 2H), 3.00 (m, 2H), 1.35 (t, 3H); Anal. Calcd. for C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>O<sub>6</sub>S: C, 54.29; H, 4.10; N, 12.66; S, 7.23. Found: C, 53.71; H, 4.41; N, 12.56; S, 7.14.

15      **[00191]**      Step 4

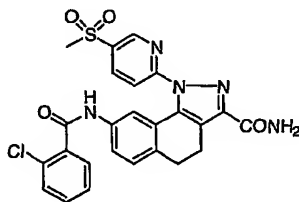
The product from step 3 (1.6 g, 0.0036 mol) was hydrogenated in a Parr shaker with 20% Pd(OH)<sub>2</sub>/C in acetic acid for 2 h at 5 psi. After the removal of solvent, the residue was triturated with a mixture of methanol and ether to give 1.0 g of the product as a white solid (67% yield): <sup>1</sup>HNMR (DMSO, 400 MHz) δ: 9.01 (dd, 1H), 8.62 (dd, 1H), 8.07 (dd, 1H), 7.01 (d, 1H), 6.46 (dd, 1H), 6.12 (d, 1H), 4.90 (brs, 2H), 4.33 (q, 2H), 3.42 (s, 3H), 2.87 (m, 2H), 2.78 (m, 2H), 1.33 (t, 3H); Anal. Calcd. for C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>S: C, 58.24; H, 4.89; N, 13.58; S, 7.77. Found: C, 57.70; H, 4.68; N, 13.43; S, 7.60.

20

25

**[00192]**      Step 5

To a suspension of the product from step 4 (0.95 g, 0.0023 mol) in 25 mL of  
5 methanol was added liquid ammonia through a dry-ice condenser. The solution was  
sealed with a septum and stirred at room temperature for 48 h. Solvent was  
removed and the solid was triturated with methanol to give 0.68 g of product as a  
yellow solid (77% yield): <sup>1</sup>HNMR (CDCl<sub>3</sub>, 400 MHz) δ: 8.99 (d, 1H), 8.63 (ddd,  
1H), 8.10 (d, 1H), 7.66 (s, 1H), 7.43 (s, 1H), 7.00 (d, 1H), 6.45 (d, 1H), 6.22 (s,  
10 1H), 4.89 (s, 2H), 3.41 (s, 3H), 2.86 (m, 2H), 2.74 (m, 2H); Anal. Calcd. for  
C<sub>18</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>S: C, 56.39; H, 4.47; N, 18.27; S, 8.36. Found: C, 55.48; H, 4.29; N,  
17.84; S, 8.19.

**[00193]**      Step 6

15

To a suspension of the product from step 5 (0.62 g, 0.0016 mol) in 10 mL of  
pyridine was added 2-chlorobenzoyl chloride (0.29 g, 0.0016 mol) in one portion  
and the reaction mixture was stirred at room temperature overnight. Solvent was  
20 removed and the residue was partitioned between ethyl acetate and water. The  
organic phase was washed with brine, dried over MgSO<sub>4</sub>, and filtered. The filtrate  
was concentrated and purified by chromatography on silica gel (ethyl acetate) to  
give 0.6 g of the product as a yellow solid (72% yield); <sup>1</sup>HNMR (DMSO, 400 MHz)  
δ: 10.36 (s, 1H), 9.00 (d, 1H), 8.62 (dd, 1H), 8.15 (d, 1H), 7.74 (s, 1H), 7.39-7.54  
25 (m, 7 H), 7.34 (d, 1H), 3.32 (s, 3H), 2.93 (m, 4H); Anal. Calcd. for C<sub>25</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>4</sub>S:

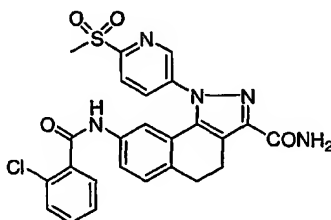


C, 57.53; H, 3.86; N, 13.42; S, 6.14. Found: C, 56.69; H, 4.37; N, 12.82; S, 5.86.

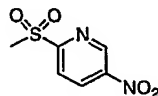
IKK-2 resin  $IC_{50} \leq 1 \mu M$ .

[00194] Example 368

5 8-[(2-chlorobenzoyl)amino]-1-[6-(methylsulfonyl)pyridin-3-yl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



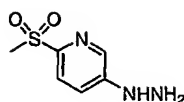
10 [00195] Step 1



A mixture of 2-chloro-5-nitropyridine (20.5 g, 0.13 mol) and sodium thiomethoxide (10.9 g, 0.16 mol) in DMS was heated at 100°C under nitrogen for 3 h. Cooled to room temperature and water was added. The precipitate was collected, air-dried to give 14.5 g of product as a brown solid. To a solution of this solid (16.5 g, 0.097 mol) in 100 mL of acetone was added 170 mL of 2N sulfuric acid solution. Then a solution of  $KMnO_4$  (20.0 g, 0.126 mol) in 375 mL of water was added dropwise to the above suspension. The reaction mixture was stirred at RT overnight and then it was filtered. The solid was stirred with 400 mL of hot ethanol, then cooled and filtered. The filtrate was concentrated to half volume and the precipitate was collected and air-dried to give 12.5 g of the desired product as a pale yellow solid, which was used without further purification. The NMR and MS were consistent with the proposed structure.

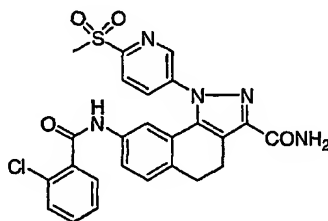
25

[00196]      Step 2



A mixture of the product from step 1 (12.3 g, 0.061 mol), iron (6.5 g, 0.11 mol) and  
5      1 mL of acetic acid in 250 mL of water was heated at reflux for 4 h. Cooled to  
room temperature, 400 mL of sat. NaHCO<sub>3</sub> solution was added and extracted with  
ethyl acetate. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and  
concentrated to give 3.5 g of crude as a dark brown solid. To a solution of this  
crude in conc. HCl at -10°C was added a solution of NaNO<sub>2</sub> dropwise. The mixture  
10      was stirred at this temperature for 2 h and then a solution tin chloride in conc. HCl  
was added slowly to keep the temperature under -5°C. The reaction was stirred  
overnight while allowing to warm up to RT. NaOH solution was added to adjust  
pH to 9 and filtered through a pad of Celite®. The aqueous phase was extracted  
with THF and the organic layer was washed with brine, dried over MgSO<sub>4</sub>, and  
15      concentrated. The crude was triturated with methanol to give the hydrazine as a  
yellow solid. The NMR and MS were consistent with the proposed structure.

[00197]      Steps 3-6

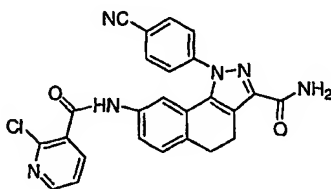


20

The title compound was synthesized by using the same procedure from step 3 to  
step 6 for Example 367 except using the above hydrazine; <sup>1</sup>H NMR (DMSO, 400  
MHz) 10.38 (s, 1H), 9.08 (s, 1H), , 1H), 8.41 (d, 1H), 8.25 (d, 1H), 7.71 (s, 1H),  
7.35–7.53 (m, 8H), 3.28 (s, 3H), 2.96 (m, 4H); Anal. Calcd. for C<sub>25</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>4</sub>S: C,  
25      57.53; H, 3.86; N, 13.42; S, 6.14. Found: C, 56.62; H 4.09; N, 13.09; S, 5.99.  
IKK-2 resin IC<sub>50</sub> ≤ 1 μM.

**[00198] Example 369**

8-[(2-chlorobenzoyl)amino]-1-(4-cyanophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



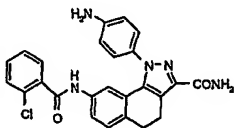
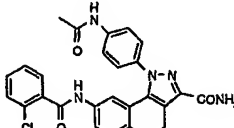
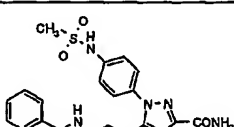
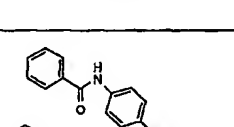
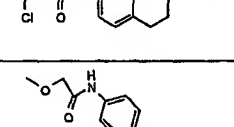
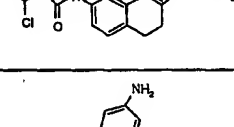
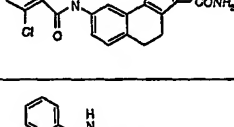
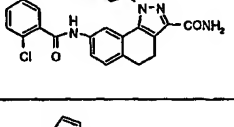
5

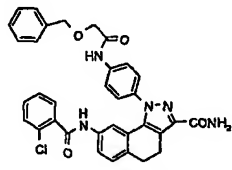
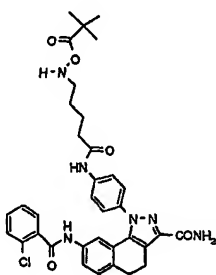
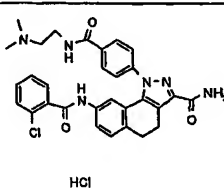
1-(4-Bromophenyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (5.2g) and  $\text{Zn}(\text{CN})_2$  (0.9g) were dissolved in 100ml DMF under  $\text{N}_2$ . Then  $\text{Pd}(\text{Ph}_3\text{P})_4$  (1.38g) was added. The reaction mixture was heated up to 100°C under  $\text{N}_2$  for 12 hours. After the reaction is completed by HPLC, the solvent was evaporated, and the residue was suspended in ethyl acetate and water. After filtration, and washing with water and ethyl acetate, the filtrate of the organic layer was separated and dried with  $\text{Na}_2\text{SO}_4$ . After filtration and evaporation of solvent, the residue was triturated with ether. Solid obtained was filtered and washed with ether, then dried under vacuum. The desired compound (3.4g) was obtained and characterized by  $^1\text{H}$  NMR, LC-MS (468, M+1), and CHN analysis. IKK-2 resin  $\text{IC}_{50} \leq 1 \mu\text{M}$ .

**[00199]** The compounds of Examples 370-380 in the Table 15 were prepared by the reduction and/or acylation or sulfonation from either Example 324 or Example 325 using standard conditions. The bioactivity in the IKK2 Resin assay for the compounds of Examples 370-380 is shown in Table 15.

20

Table 15

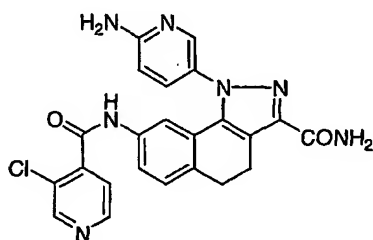
Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	457.92	1-(4-aminophenyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	458	370
	499.96	1-[4-(acetlamino)phenyl]-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	500	371
	536.01	8-[(2-chlorobenzoyl)amino]-1-[4-[(methylsulfonyl)amino]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	536	372
	562.03	1-[4-(benzoylamino)phenyl]-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	562	373
	529.99	8-[(2-chlorobenzoyl)amino]-1-[4-[(methoxyacetyl)amino]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	530	374
	457.92	1-(3-aminophenyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	458	375
	596.48	8-[(2-chlorobenzoyl)amino]-1-[4-[(2-chlorobenzoyl)amino]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	596	376
	507.98	8-[(2-chlorobenzoyl)amino]-1-[4-(1H-pyrrol-1-yl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	508	377

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	606.09	1-(4-[(benzyloxy)acetyl]amino)phenyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	606	378
	657.18	8-[(2-chlorobenzoyl)amino]-1-{4-[(5-[(2,2-dimethylpropanoyl)oxy]amino)pentanoyl]amino}phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	657	379
 HCl	593.52	8-[(2-chlorobenzoyl)amino]-1-[4-[(2-(dimethylamino)ethyl)amino]carbonyl]phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	1 ≤ 10 μM	557	380

[00200] Example 381

1-(6-aminopyridin-3-yl)-8-[(3-chloroisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

5



[00201] Step 1: A 100 mL 3-neck flask was charged with (in order) CuI (300 mg, 1.6 mmol), 1,10-phenanthroline (350 mg, 1.94 mmol) and 25 mL DMF. A dark cherry red solution resulted. To this solution was added (in order) 2-Chloro-5-iodopyridine (2.0 g, 8.4 mmol), t-butyl carbamate (1.33 g, 10.1 mmol), 25 mL DMF

10

and  $\text{Cs}_2\text{CO}_3$  (4.75 g, 14.6 mmol). To the flask was attached a reflux condenser with a nitrogen inlet, a thermometer and a glass stopper. With stirring the slurry was heated to  $70^\circ\text{C}$  for 3 h. The reaction was allowed to cool to room temperature. The crude reaction mixture was poured into 200 mL water giving a rust colored solid.

5 The product was extracted from this aqueous slurry using 2 x 200 mL diethyl ether. The ether layers were extracted with 200 mL water, dried over  $\text{MgSO}_4$ , filtered, and then concentrated giving a dark oil. The oil was chromatographed on silica gel (25g) using 20% EtOAc/80% hexane giving 0.9 g (3.7 mmol, 44%) of product (light yellow oil which slowly solidified). NMR and MS were consistent with the

10 proposed structure.

[00202] Step 2: To a mixture of the product from step 1 (6.35 g, 0.023mol) and ethyl (7-nitro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)(oxo)acetate (6.6 g, 0.023 mol) in 200 mL of ethanol was added 10 mL of 1N HCl and the reaction

15 mixture was heated at reflux under nitrogen for 6 h. After the solution was cooled, the precipitate was collected by filtration and air-dried to give 7.5 g of the product as a yellow crystal (83% yield);  $^1\text{HNMR}$  (DMSO, 400 MHz)  $\delta$ : 8.76 (dd, 1H), 8.22 (dd, 1H), 8.12 (dd, 1H), 7.85 (dd, 1H), 7.71 (d, 1H), 7.44 (d, 1H), 4.35 (q, 2H), 3.14 (m, 2H), 3.03 (m, 2H), 1.33 (t, 3H); Anal. Calcd. for  $\text{C}_{19}\text{H}_{15}\text{ClN}_4\text{O}_4$ : C, 57.22; H, 3.79; N, 14.05; Cl, 8.89. Found: C, 57.03; H, 3.95; N, 13.71; Cl, 9.04.

20

[00203] Step 3: The product from step 2 (7.5 g, 0.019 mol) was hydrogenated in a Parr shaker with 5% Pt/C in acetic acid for 2 h at 5 psi. After the removal of solvent, the residue was triturated with a mixture of methanol and ether

25 to give 6.5 g of the product as a pale yellow solid (94% yield):  $^1\text{HNMR}$  (DMSO, 400 MHz)  $\delta$ : 8.64(dd, 1H), 8.09 (dd, 1H), 7.75 (dd, 1H), 7.02 (d, 1H), 6.45 (dd, 1H), 6.03 (d, 1H), 4.99 (brs, 2H), 4.31 (q, 2H), 2.88 (m, 2H), 2.78 (m, 2H), 1.31 (t, 3H); Anal. Calcd. for  $\text{C}_{19}\text{H}_{17}\text{ClN}_4\text{O}_2$ : C, 61.88; H, 4.65; N, 15.19; Cl, 9.61. Found: C, 60.97; H, 5.06; N, 14.65; Cl, 9.50.

30

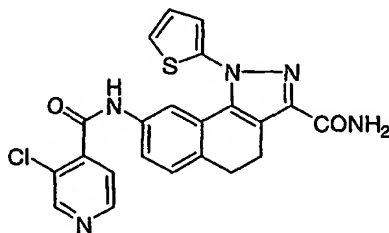
[00204] Step 4: To a mixture of the product from step 3 (0.96 g, 0.0026 mol) and 3-chloroisonicotinic acid (0.65 g, 0.004 mol) in 25 mL of DMF was added 1 mL

of diisopropylethylamine, followed by the addition of HATU (1.50 g, 0.004 mol). The reaction was stirred at room temperature for 16 h and concentrated. The residue was triturated with methanol and acetonitrile to give 1.08 g of product as a pale yellow solid (82% yield); <sup>1</sup>HNMR (DMSO, 400 MHz) δ: 10.56 (s, 1H), 8.76 (s, 1H), 8.69 (d, 1H), 8.63 (d, 1H), 8.14 (dd, 1H), 7.76 (d, 1H), 7.56 (d, 1H), 7.53 (dd, 1H), 7.40 (d, 1H), 7.26 (d, 1H), 4.32 (q, 2H), 2.97 (s, 4H), 1.31 (t, 3H).

[00205] Step 5: A sealed reaction vessel containing the product from step 4 (0.8 g, 0.0016 mol) and 10 mL of liquid ammonia in 50 mL of absolute alcohol was heated at 120°C and 600 psi for 24 h. After cooling, solvent was removed and the residue was triturated with a mixture of methanol and acetonitrile to give 0.38 g of product as a pale yellow solid (52% yield); <sup>1</sup>HNMR (DMSO, 400 MHz) δ: 10.57 (s, 1H), 8.75 (s, 1H), 8.63 (d, 1H), 8.02 (d, 1H), 7.47-7.56 (m, 3H), 7.35 (d, 1H), 7.32 (d, 1H), 7.27 (s, 1H), 6.54 (d, 1H), 6.36 (s, 2H), 2.92 (m, 4H); Anal. Calcd. for C<sub>23</sub>H<sub>18</sub>ClN<sub>7</sub>O<sub>2</sub>: C, 60.07; H, 3.95; N, 21.32. Found: C, 59.26; H, 3.99; N, 20.85.

[00206] Example 382

8-[(3-chloroisonicotinoyl)amino]-1-thien-2-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



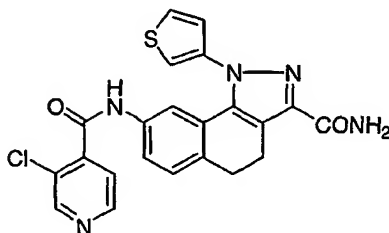
[00207] Step 1: To a mixture of *tert*-butyl 1-thien-2-ylhydrazinecarboxylate (3.9 g, 0.016 mol, synthesized by using the same method as the previous example) and ethyl (7-nitro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)(oxo)acetate (4.6 g, 0.016 mol) in 100 mL of ethanol was added 5 mL of 1N HCl and the reaction mixture was heated at reflux under nitrogen for 6 h. After the solution was cooled, the precipitate was collected by filtration and air-dried to give 2.6 g of the product

as a brown solid (44% yield). This solid was refluxed with 3eq of tin chloride in ethanol under nitrogen for 3 h. Solvent was removed and the residue was partitioned between THF and sat. NaHCO<sub>3</sub> solution. Organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give 1.4 g of crude as a yellow solid, used without further purification. The MS and NMR were consistent with the proposed structure.

[00208] Step 2: A sealed reaction vessel containing the crude product from step 1 (1.3 g, 0.004 mol) and 10 mL of liquid ammonia in 50 mL of absolute alcohol was heated at 120°C and 600 psi for 24 h. After cooling, solvent was removed and the residue was triturated with a mixture of methanol and acetonitrile to give 1.0 g of product as a pale yellow solid. To a mixture of this solid (0.56 g, 0.0018 mol) and 3-chloroisonicotinic acid (0.39 g, 0.0027 mol) in 20 mL of DMF was added 1 mL of diisopropylethylamine, followed by the addition of HATU (1.03 g, 0.0027 mol). The reaction was stirred at room temperature for 16 h and concentrated. The residue was triturated with methanol and water to give 0.31 g of product as pale yellow solid (38% yield); <sup>1</sup>HNMR (DMSO, 400 MHz) δ: 10.55 (s, 1H), 8.75 (s, 1H), 8.62 (d, 1H), 7.67 (d, 1H), 7.62 (s, 1H), 7.55 (d, 1H), 7.44 (s, 3H), 7.42 (s, 1H), 7.35 (m, 3H), 7.12 (m, 1H), 2.93 (m, 4H); Anal. Calcd. for C<sub>22</sub>H<sub>16</sub>ClN<sub>5</sub>O<sub>2</sub>S: C, 58.73; H, 3.58; N, 15.57. Found: C, 58.26; H, 3.62; N, 15.48.

[00209] Example 383

8-[(3-chloroisonicotinoyl)amino]-1-thien-3-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

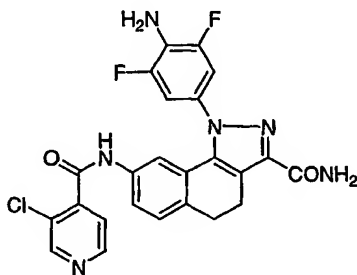




This compound was synthesized by using the same method as previously described in Example 381. <sup>1</sup>HNMR (DMSO, 400 MHz)  $\delta$ : 10.54 (s, 1H), 8.75 (s, 1H), 8.62 (d, 1H), 7.85 (dd, 1H), 7.75 (dd, 1H), 7.58 (s, 1H), 7.54 (d, 1H), 7.38 (m, 3H), 7.31 (s, 1H), 7.28 (dd, 1H), 2.92 (m, 4H); Anal. Calcd. for C<sub>22</sub>H<sub>16</sub>ClN<sub>5</sub>O<sub>2</sub>S: C, 58.73; H, 3.58; N, 15.57. Found: C, 58.65; H, 3.77; N, 15.59.

**[00210] Example 384**

1-(4-amino-3,5-difluorophenyl)-8-[(3-chloroisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



**[00211] Step 1:** 1-Bromo- 3,4,5 trifluorobenzene (5 g, 24 mmol) was added to a slurry of Pd(OAc)<sub>2</sub> (0.269 g, 5 mol %), bisdiphenylphosphino-ferrocene (1.0 g, 7 mol %) in anhydrous toluene (50 mL) at rt. Benzophenone hydrazone (4.9 g) was added, stirred for 5 min following by addition of dried cesium acetate (9.33 g) and toluene (40 mL). The flask was removed from a glove box and heated to 86 °C for 72 hours. The reaction was monitored by disappearance of bromotrifluorobenzene by LC (210 nm) or <sup>19</sup>F NMR. The reaction mixture was cooled down to room temperature and filtered through a sintered glass funnel. The solvent was removed under the vacuum. The orange solid residue was re-dispersed in ether (15 mL) and hexane (150 mL) and heated up to 58 °C, stirred for 20 min. The hot solution was quickly filtered, solid discarded and the solution was allowed to cool to room temperature, stirred for 30 min, then 1 hour at 4 °C. The formed slurry was filtered, washed with cold hexane (2x25 mL). Crystals were dried in air then in the vacuum

at 80 °C for 1 hour to give 5 g of diphenylmethanone (3,4,5-trifluorophenyl)hydrazone (64 % yield) as a yellowish solid.

[00212]      Step 2: The product from step 1 (1.9 g) and ethyl (7-nitro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)(oxo)acetate (1.66 g) were dispersed in 1M HCl in ethanol (125 mL), heated to reflux, and stirred until the starting material disappeared (overnight). The solution was cooled down to 4 °C and stirred for 2 hrs. The cold slurry was filtered, solid washed with anhydrous ethanol (2x25 mL), dried on air and in the vacuum oven at 70°C for 1 hour to give 1.4 g of 8-nitro-1-(3,4,5-trifluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide as a brown powder (58 % yield).

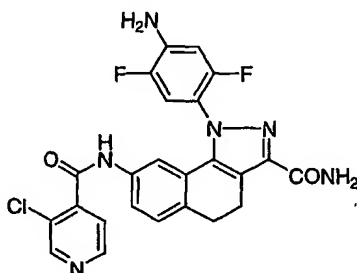
[00213]      Step 3: The product from step 2 (1.17 g, 0.0028mol) was hydrogenated in a Parr shaker with 5% Pt/C in acetic acid for 4 h at 5 psi. After the removal of solvent, the residue was triturated with a mixture of methanol and ether to give 1.0 g of the product as a pale yellow solid. A sealed reaction vessel containing this solid and 10 mL of liquid ammonia in 50 mL of absolute alcohol was heated at 120°C and 600 psi for 24 h. After cooling, solvent was removed and the residue was triturated with a mixture of methanol and acetonitrile to give 0.8 g of 8-amino-1-(4-amino-3,5-difluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide as a pale yellow solid (80% yield over two steps); NMR spectrum was consistent with the proposed structure.

[00214]      Step 4: To a mixture of the product from step 3 (0.75 g, 0.0021 mol) and 3-chloroisonicotinic acid (0.33 g, 0.0023 mol) in 20 mL of DMF was added 1 mL of diisopropylethylamine, followed by the addition of HATU (0.9 g, 0.0023 mol). The reaction was stirred at room temperature for 16 h and concentrated. The crude was purified by reverse phase HPLC to give 0.15 g of 1-(4-amino-3,5-difluorophenyl)-8-[(3-chloroisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide as a pale white solid (15% yield); <sup>1</sup>HNMR (DMSO, 400 MHz) δ: 10.56 (s, 1H), 8.76 (s, 1H), 8.63 (d, 1H), 8.56 (s, 1H), 7.54 (d, 1H), 7.49 (dd, 1H), 7.35 (m, 2H), 7.31 (s, 1H), 6.71 (m, 2H), 5.88 (s, 2H), 2.92

(m, 4H); Anal. Calcd. for  $C_{24}H_{17}FCIN_6O_2 + 0.5 H_2O$ : C, 57.21; H, 3.60; N, 16.68. Found: C, 56.91; H, 3.70; N, 16.64.

**[00215] Example 385**

- 5 1-(4-amino-2,5-difluorophenyl)-8-[(3-chloroisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



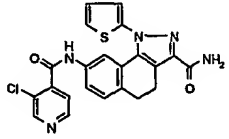
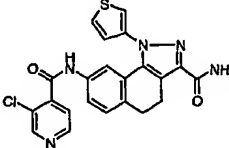
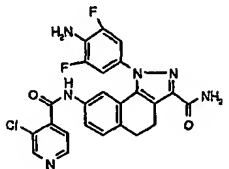
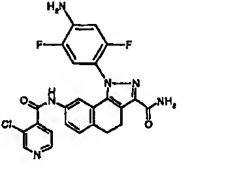
- 10 **[00216]** This compound was synthesized by using the same method as Example 384; mp: 289-290°C;  $^1H$ NMR (DMSO, 400 MHz)  $\delta$ : 10.55 (s, 1H), 8.75 (s, 1H), 8.63 (d, 1H), 7.57 (d, 1H), 7.55 (s, 1H), 7.39 (m, 4H), 7.29 (s, 1H), 6.70 (m, 1H), 5.90 (brs, 2H), 2.89(s, 4H); Anal. Calcd. for  $C_{24}H_{17}FCIN_6O_2$ : C, 58.25; H, 3.46; N, 16.98. Found: C, 57.65; H, 3.73; N, 16.82.

15

**[00217]** Additional analytical data is presented in Table 16 for the compounds of Examples 381-385.

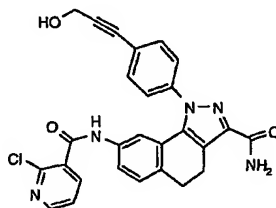
Table 16

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	459.90	1-(6-aminopyridin-3-yl)-8-[(3-chloroisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu M$	460	381

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	449.92	8-[(3-chloroisonicotinoyl)amino]-1-thien-2-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	450	382
	449.92	8-[(3-chloroisonicotinoyl)amino]-1-thien-3-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	450	383
	494.89	1-(4-amino-3,5-difluorophenyl)-8-[(3-chloroisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	495	384
	494.89	1-(4-amino-2,5-difluorophenyl)-8-[(3-chloroisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	495	385

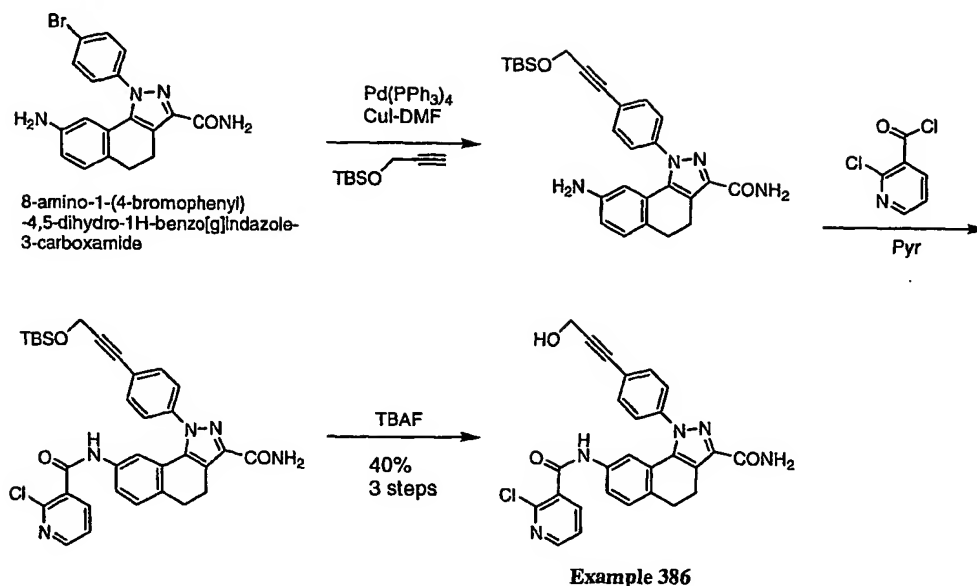
**[00218] Example 386**

8-[[[(2-chloropyridin-3-yl)carbonyl]amino]-1-[4-(3-hydroxyprop-1-ynyl)phenyl]-  
5 4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



The following scheme was used for the synthesis of the title compound of Example  
10 386.

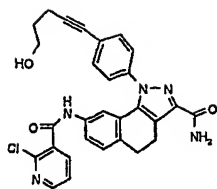
## SCHEME XXVIII



A stirred solution of 8-amino-1-(4-bromophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (2.30 g, 6 mmol) and *tert*-butyldimethyl-(2-propynyl-oxy)silane (1.12 g, 6.6 mmol) in DMF-triethylamine (6 mL-6 mL) was added CuI (114 mg, 0.6 mmol) and tetrakis(triphenylphosphine) palladium (346 mg, 0.3 mmol) and the resulted mixture was heated at 100 °C for 14 h before cooled to rt. The mixture was filtered through silica gel pad, washed with EtOAc, and concentrated. The crude material was taken into pyridine (20 mL), treated 2-chloronicotinyl chloride (1.23g, 7 mmol) at RT for 14 h. Tetrabutylammonium fluoride (25 mL of 1M THF solution, 25 mmol) was added at RT and stirred overnight. Aqueous ammonium chloride was added, the mixture extracted with EtOAc (5x30 mL). The organic portions were combined, dried over MgSO<sub>4</sub>, filtered, and separated by silica gel column (EtOAc). This gave 8-([(2-chloropyridin-3-yl)carbonyl]amino)-1-[4-(3-hydroxyprop-1-ynyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide as a pale yellow solid (1.19g, 40% over 3 steps). <sup>1</sup>H NMR was consistent with its structure.

**[00219] Example 387**

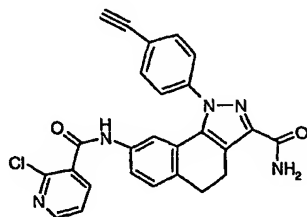
8-([(2-chloropyridin-3-yl)carbonyl]amino)-1-[4-(5-hydroxypent-1-ynyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



The compound was prepared in a similar manner as Example 386. <sup>1</sup>H NMR was  
 5 consistent with its structure.

[00220] Example 388

8-{[(2-chloropyridin-3-yl)carbonyl]amino}-1-(4-ethynylphenyl)-4,5-dihydro-1H-  
 benzo[g]indazole-3-carboxamide

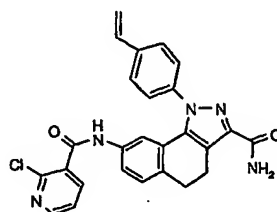


A stirred solution of 8-amino-1-(4-bromophenyl)-4,5-dihydro-1H-  
 15 benzo[g]indazole-3-carboxamide (5.74 g, 15 mmol) and *tert*-  
 butyldimethylsilylacetylene (2.31 g, 16.5 mmol) in DMF-triethylamine (20 mL-10  
 mL) was added CuI (285 mg, 1.5 mmol) and tetrakis(triphenylphosphine) palladium  
 (870 mg, 0.75 mmol) and the resulted mixture was heated at 100 °C for 14 h before  
 cooled to rt. The mixture was filtered through silica gel pad, washed with EtOAc,  
 20 and concentrated. The crude material was taken into pyridine (30 mL), treated with  
 2-chloronicotinyl chloride (2.90 g, 16.5 mmol) at RT for 14 h. Tetrabutylammonium fluoride (25 mL of 1M THF solution, 25 mmol) was added at  
 RT and stirred overnight. Aqueous ammonium chloride was added, the mixture  
 extracted with EtOAc (5x30 mL). The organic portions were combined, dried over  
 25 MgSO<sub>4</sub>, filtered, and separated by silica gel column (EtOAc). This gave product as

a pale yellow solid (3.5 g, 49% over 3 steps).  $^1\text{H}$  NMR was consistent with its structure. CNH calculated for  $\text{C}_{26}\text{H}_{18}\text{N}_5\text{O}_2\text{Cl}(\text{H}_2\text{O})_{1.3}$ : C(63.5%), H(4.2%), N(14.3%); found: C(63.6%), H(4.0%), N(14.3%).

5 [00221] Example 389

8-[[[(2-chloropyridin-3-yl)carbonyl]amino]-1-(4-vinylphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



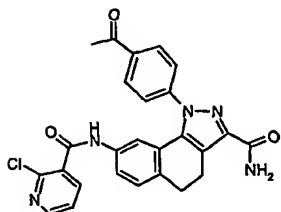
10

A solution of 8-[[[(2-chloropyridin-3-yl)carbonyl]amino]-1-(4-ethynylphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (557 mg, 1.19 mmol) in DMF-DMSO (20 mL – 1 mL) was treated at RT with  $\text{H}_2$  (5 psi) and Pd- $\text{CaSO}_4$  (5%, 100 mg) for 12 min. The mixture was filtered through celite pad, concentrated and added water.

15 The solid product was collected via filtration, washed with water and ether, and dried to give product (262 mg, 47%).  $^1\text{H}$  NMR was consistent with its structure.

[00222] Example 390

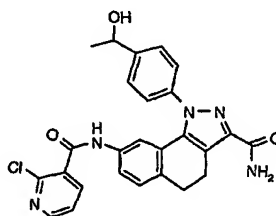
1-(4-acetylphenyl)-8-[[[(2-chloropyridin-3-yl)carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



A mixture of 8-[[2-chloropyridin-3-yl]carbonyl]amino}-1-(4-ethynylphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (442 mg, 1.2 mmol), water (65 mg, 3.6 mmol), and triflic acid (270 mg, 1.8 mmol) in dioxane (10 mL) was heated to 100 °C for 18 h. The mixture was cooled to RT, aqueous NaHCO<sub>3</sub> was added, and filtered. The product was washed with water and ether, and dried. This gave product (293 mg, 67%). <sup>1</sup>H NMR was consistent with its structure.

[00223] Example 391

8-[[2-chloropyridin-3-yl]carbonyl]amino}-1-[4-(1-hydroxyethyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

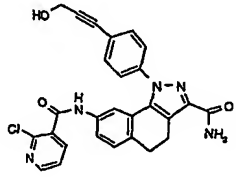
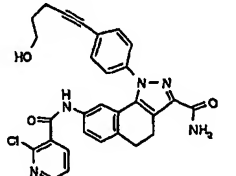
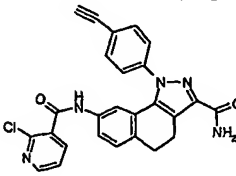
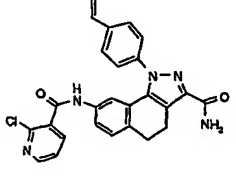
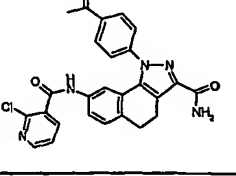
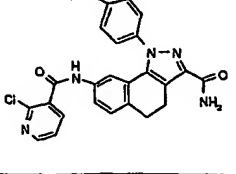


A mixture of 1-(4-acetylphenyl)-8-[[2-chloropyridin-3-yl]carbonyl]amino}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (200 mg, 0.41 mmol) in MeOH (3 mL) and water (0.3 mL) was added NaBH<sub>4</sub> (10 mg, 0.25 mmol) at RT and stirred for 14 h. The mixture was separated on silica gel column (EtOAc) to give product (100 mg, 50%). <sup>1</sup>H NMR was consistent with its structure.

[00224] Additional analytical data for the compounds of Examples 386-391 is presented in Table 17

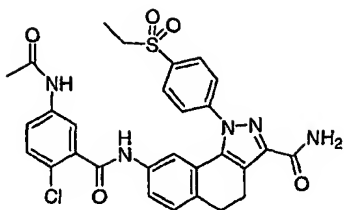


Table 17.

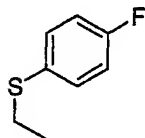
Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	MS (M+H)	Example
	497.94	8-([(2-chloropyridin-3-yl)carbonyl]amino)-1-[4-(3-hydroxyprop-1-ynyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	498	386
	525.99	8-([(2-chloropyridin-3-yl)carbonyl]amino)-1-[4-(5-hydroxypent-1-ynyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	526	387
	467.91	8-([(2-chloropyridin-3-yl)carbonyl]amino)-1-(4-ethynylphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	468	388
	469.93	8-([(2-chloropyridin-3-yl)carbonyl]amino)-1-(4-vinylphenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	470	389
	485.93	1-(4-acetylphenyl)-8-([(2-chloropyridin-3-yl)carbonyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	486	390
	487.95	8-([(2-chloropyridin-3-yl)carbonyl]amino)-1-[4-(1-hydroxyethyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	488	391

## [00225] Example 392

- 5 8-[[5-(acetylamino)-2-chlorobenzoyl]amino]-1-[4-(ethylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



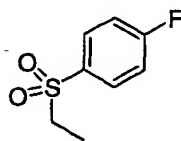
5 [00226] Step 1



10 To a stirring solution of NaOH (11.26 g, 281.6 mmol) in water (500 mL) was added dropwise a solution of 4-fluorothiophenol (25 mL, 234.6 mmol) in methanol (50 mL). After 15 minutes ethyl bromide (14.4 mL, 281.6 mmol) was added. After 6 hours more NaOH (1 g) was added and the reaction mixture was extracted with ether (3 X 300 mL). The combined organic extracts were treated with brine followed by MgSO<sub>4</sub> then concentrated down to give 1-(ethylthio)-4-fluorobenzene (29 g, 80%) as a slightly yellow colored liquid.

15

[00227] Step 2

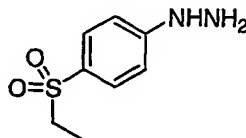


20 To a solution of the crude product of step 1 in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) was added *m*-CPBA (82 g of 77% max powder, 368 mmol) portion-wise with vigorous stirring. After 5 hours the reaction mixture was concentrated down and ethyl acetate (750 mL) was added. The organic phase was then washed with 4% aqueous NaOH (2 X 100 mL), water (100 mL), then brine (75 mL), and finally dried over

MgSO<sub>4</sub>. The solution was concentrated down to yield a white solid (17.9 g) that was carried onto the next step without purification.

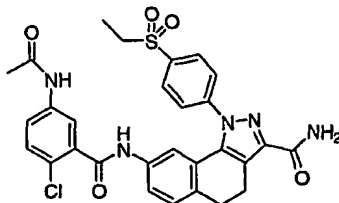
[00228] Step 3

5



The crude product of step 2 was dissolved in ethanol (200 mL) and hydrazine (24 mL, 758 mmol) was added. The reaction mixture was heated to reflux for 6 hours then left at room temperature overnight. The ethanol was concentrated down to a smaller volume then water was added. A white precipitate formed and was collected (12.87 g, 68%). The desired compound (1-[4-(ethylsulfonyl)phenyl]hydrazine) was used in the next step without purification.

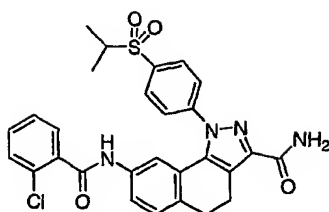
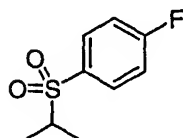
15 [00229] Step 4



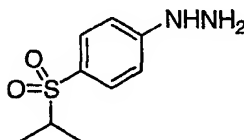
The title compound was prepared in a manner analogous to Example 3 using 1-[4-(ethylsulfonyl)phenyl]hydrazine and the appropriate acylating agent. The desired product crystallizes out of the reaction media in 81% yield. Anal. Calcd for C<sub>29</sub>H<sub>26</sub>ClN<sub>5</sub>O<sub>5</sub>S (MW = 591.13): C, 58.83; H, 4.43; N, 11.83. Found: C, 58.69; H, 4.46; N, 12.16.

[00230] Example 393

25 8-[(2-chlorobenzoyl)amino]-1-[4-(isopropylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

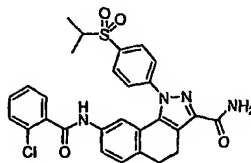
5 [00231] Step 1

To a 250 mL round-bottomed flask was placed KH (35 wt % in mineral oil) (1.64 g, 14.35 mmol). The solid was washed with hexane (2 X 10 mL) under nitrogen. THF (50 mL) was added and the suspension was cooled to 0 °C. Iodomethane (0.89 mL, 14.35 mmol) followed by a solution of 4-fluorophenylmethylsulfone (1.25 g, 7.17 mmol) in THF (10 mL) was added. The reaction mixture was stirred at 0 °C for 1 hour then allowed to warm to room temperature overnight. A mixture of ethyl and isopropyl sulfone was observed, so LiHMDS (7.2 mL, 14.35 mmol) and iodomethane (0.45 mL, 14.35 mmol) were added. After 2.5 hours water was added to the reaction mixture and the aqueous phase was extracted with ether (3 X 150 mL). The combined organic extracts were treated with brine and dried over MgSO<sub>4</sub>. The ether solution was concentrated down to give the desired compound as a yellow solid. The crude material was used in the next step without further purification.

[00232] Step 2

The product of step 1 (640 mg, 3.15 mmol) was dissolved in absolute ethanol (12 mL), the system was flushed with N<sub>2</sub> and hydrazine (404 mg, 12.6 mmol) was added and the reaction refluxed overnight. HPLC showed 78% product and 21% starting material. To drive the reaction to completion 2 equivalents of additional hydrazine was added and reaction was refluxed for additional 5 hours, at this time HPLC indicated 95% product. The reaction mixture was concentrated and the residue was stirred with water. A white solid, 390 mg (58%) was isolated. HPLC indicated 86% product and 14% starting material. The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The organic phase was dried over MgSO<sub>4</sub>, and concentrated to yield 258 mg (38%) of 1-[4-(isopropylsulfonyl)phenyl]hydrazine with 99% purity. MH<sup>+</sup> = 215. The 390 mg was re-dissolved in 10 mL ethanol and treated once more with additional hydrazine to obtain additional product with the desired purity.

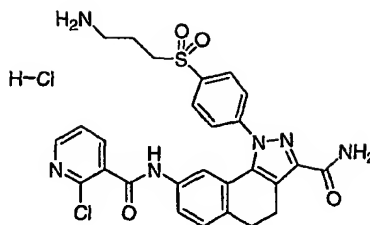
[00233] Step 3



The title compound was prepared in a manner analogous to Example 3 using 1-[4-(isopropylsulfonyl)phenyl]hydrazine and the appropriate acylating agent. The desired compound was recovered in 86% yield. HPLC indicated the compound had 94% purity. Anal. Calcd for C<sub>28</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>4</sub>S + .1 H<sub>2</sub>O (MW = 550.05): C, 61.05; H, 4.61; N, 10.17. Found: C, 60.67; H, 4.44; N, 10.14.

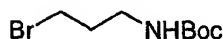
[00234] Example 394

1-{4-[(3-aminopropyl)sulfonyl]phenyl}-8-[[2-chloropyridin-3-yl]carbonyl]amino}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride



[00235] Step 1

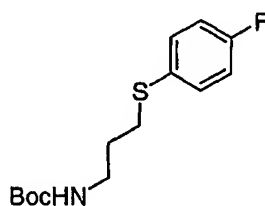
5



Commercially available 3-bromopropylamine hydrogen bromide (10 g, 45.7 mmol) was suspended in  $\text{CH}_2\text{Cl}_2$  (125 mL). Triethylamine (10 mL, 98 mmol) was added followed by  $(\text{Boc})_2\text{O}$  (11g, 50 mmol) as a solid. After stirring overnight at room temperature the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (100 mL). The organic phase was washed with 1M HCl (100 mL), sat. aq.  $\text{NaHCO}_3$  (50 mL), and brine (50 mL) then dried over  $\text{MgSO}_4$ . Evaporation under reduced pressure yielded the desired compound as a slightly yellow liquid (10.55g, 97%) and no purification was necessary.

15

[00236] Step 2

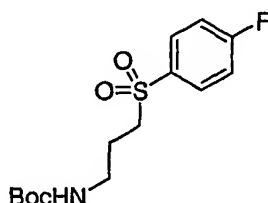


To a stirring solution of NaOH (624 mg, 15.6 mmol) in water (20 mL) was added drop-wise a solution of 4-fluorobenzenethiol (2 g, 15.6 mmol) in methanol (5 mL) at room temperature. After 30 minutes a solution of the product of step 2 (3.71 g, 15.6 mmol) in methanol (5 mL) was added drop-wise and the reaction mixture was allowed to stir at room temperature overnight. Ether (450 mL) was added and the aqueous layer separated. The organic phase was then washed successively with 1N

NaOH (75 mL), conc. aq.  $\text{NH}_4\text{Cl}$  (75 mL), and brine (50 mL). The solution was dried over  $\text{MgSO}_4$  and concentrated down to give the desired compound as a colorless liquid (3.2 g, 72%). The compound was used in the next step without further purification.

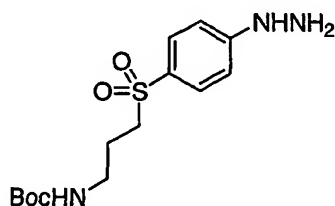
5

[00237]      Step 3



- 10 To a stirring solution of the product of step 2 (3.2 g, 11.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (150 mL) was added *m*-CPBA (77% max powder) (9.56 g, mmol) portion-wise at room temperature. The reaction was left overnight then it was concentrated down and ethyl acetate (750 mL) was added. The organic phase was then washed with 4% aqueous NaOH (2 X 100 mL), water (100 mL), then brine (75 mL), and finally
- 15 dried over  $\text{MgSO}_4$ . The solution was concentrated down to yield a white solid that was carried onto the next step without purification.

[00238]      Step 4

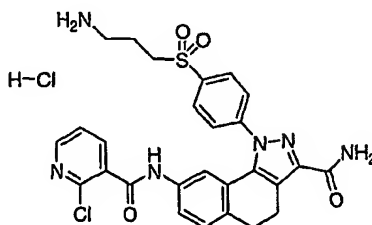


20

- [00239] All of the crude material from step 3 was dissolved in ethanol (30 mL) and hydrazine (2.4 mL, 75 mmol) was added. The reaction mixture was refluxed overnight then concentrated down to a volume of 5 mL and added to water.
- 25 The resulting precipitate was collected to yield tert-butyl 3-[(4-

hydrazinophenyl)sulfonyl]propylcarbamate as a white solid (1.88 g, 51%). The compound was used in the next step without further purification.

**[00240]**      Step 5



5

The title compound was prepared in a manner analogous to Example 3 using tert-butyl 3-[(4-hydrazinophenyl)sulfonyl]propylcarbamate and the appropriate acylating agent. The title compound was isolated as a tan colored HCl salt following standard  
10      Boc deprotection using 4N HCl in dioxane.

**[00241]**      The compounds of Examples 395-409 in Table 18 were prepared in a manner analogous to Examples 392, 393, and 394 using the appropriate hydrazine and acylating agent.

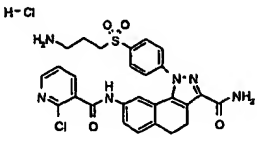
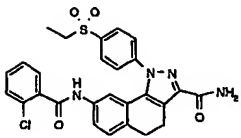
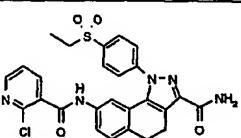
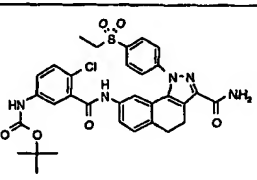
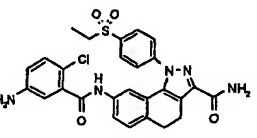
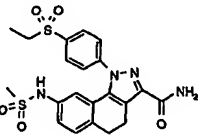
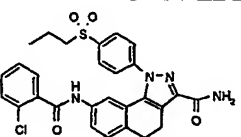
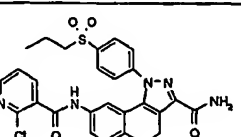
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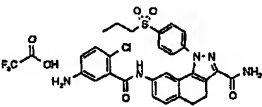
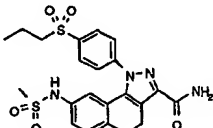
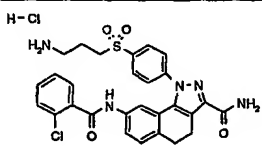
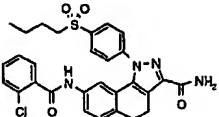
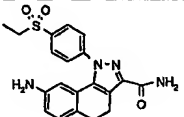
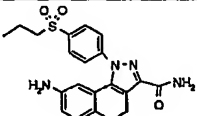
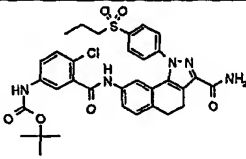
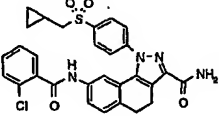
**[00242]**      The bioactivity in the IKK2 Resin assay for the compounds of Examples 392-409 is shown in Table 18.

Table 18

Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	592.08	8-[[5-(acetylamino)-2-chlorobenzoyl]amino]-1-[4-(ethylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	592	392
	550.05	8-[(2-chlorobenzoyl)amino]-1-[4-(isopropylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	550	393

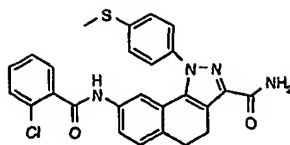
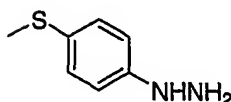


Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	601.52	1-{4-[(3-aminopropyl)sulfonyl]phenyl}-8-[(2-chloropyridin-3-yl)carbonyl]amino-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	1 ≤ 10 μM	565	394
	535.03	8-[(2-chlorobenzoyl)amino]-1-[4-(ethylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤ 1 μM	535	395
	536.01	8-[(2-chloropyridin-3-yl)carbonyl]amino-1-[4-(ethylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤ 1 μM	536	396
	650.16	tert-butyl 3-[(1-{4-(ethylsulfonyl)phenyl}-4,5-dihydro-1H-benzo[g]indazol-8-yl)amino]carbonyl-4-chlorophenylcarbamate	≤ 1 μM	650	397
	550.04	8-[(5-amino-2-chlorobenzoyl)amino]-1-[4-(ethylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤ 1 μM	550	398
	474.56	1-[4-(ethylsulfonyl)phenyl]-8-[(methylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	475	399
	549.05	8-[(2-chlorobenzoyl)amino]-1-[4-(propylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤ 1 μM	549	400
	550.04	8-[(2-chloropyridin-3-yl)carbonyl]amino-1-[4-(propylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	550	401

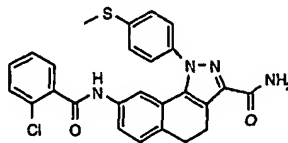
Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	678.09	8-[(5-amino-2-chlorobenzoyl)amino]-1-[4-(propylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide trifluoroacetate	$\leq 1 \mu\text{M}$	678	402
	488.59	8-[(methylsulfonyl)amino]-1-[4-(propylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	489	403
	600.53	1-[4-[(3-aminopropyl)sulfonyl]phenyl]-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$\leq 1 \mu\text{M}$	564	404
	563.08	1-[4-(butylsulfonyl)phenyl]-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	563	405
	396.47	8-amino-1-[4-(ethylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	397	406
	410.50	8-amino-1-[4-(propylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	411	407
	664.19	tert-butyl 3-[[[3-(aminocarbonyl)-1-[4-(propylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazol-8-yl]amino]carbonyl]-4-chlorophenylcarbamate	$1 \leq 10 \mu\text{M}$	664	408
	561.06	8-[(2-chlorobenzoyl)amino]-1-[4-[(cyclopropylmethyl)sulfonyl]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	561	409

## [00243] Example 410

8-[(2-chlorobenzoyl)amino]-1-[4-(methylthio)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

5 [00244] Step 1

4-Methylthiol-aniline (10.0 g; 7.2 mmol) was suspended in 6N HCl (50 mL). The solution was cooled to 0 °C and sodium nitrite (5.26 g; 7.6 mmol) dissolved in water (20 mL) was added dropwise keeping the temperature at 0 °C. When the addition is complete, the reaction mixture is homogeneous and has changed from a dark brown to an orange color. After letting this stir for an hour, SnCl<sub>2</sub>·2H<sub>2</sub>O (42.5 g; 18.8 mmol) dissolved in conc. HCl (35 mL) was added to the cold solution over a period of 15 minutes. The reaction was allowed to stir for 2 hours allowing the temperature to reach room temperature. The white solid was filtered of and suspended in ice water (300 mL). 50% NaOH solution was added till reaction mixture becomes basic (pH ~ 12). Any undissolved solid was filtered off and the aqueous phase was extracted with ethyl ether (3 x 300 mL). The organic phase was dried over MgSO<sub>4</sub> and concentrated to a yellow solid (7.8 g; 71 % yield) HPLC indicated that product is 64% pure and has M+1=155 (other impurity was starting material); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.44 (s, 3H), 6.78 (m, 2 H), 7.23 (m, 2H).

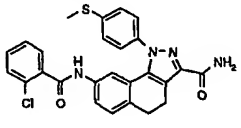
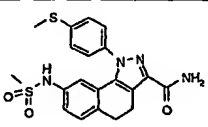
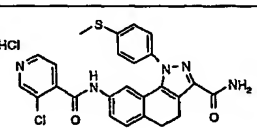
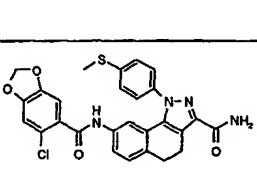
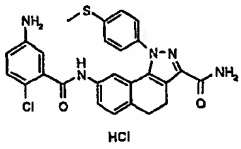
[00245] Step 2

The title compound was prepared in a manner analogous to Example 3 using 1-[4-methylsulfonyl)phenyl]hydrazine and the appropriate acylating agent.

**[00246]** The compounds of Examples 411-414 in Table 19 were prepared in a manner analogous to Examples 410 using the appropriate acylating agent.

**[00247]** The bioactivity in the IKK2 Resin assay for the compounds of Examples 410-414 is shown in Table 19.

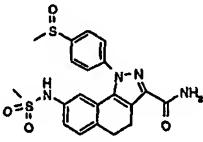
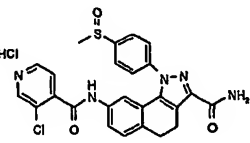
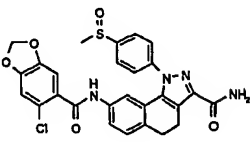
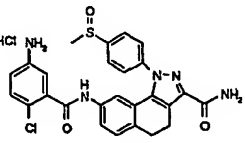
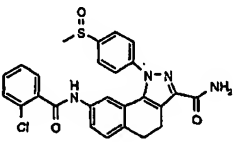
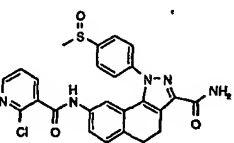
Table 19

Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	489.00	8-[(2-chlorobenzoyl)amino]-1-[4-(methylthio)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	489	410
	428.54	8-[(methylsulfonyl)amino]-1-[4-(methylthio)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	429	411
	526.45	8-[(3-chloroisonicotinoyl)amino]-1-[4-(methylthio)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$\leq 1 \mu\text{M}$	490	412
	533.01	8-[[[(6-chloro-1,3-benzodioxol-5-yl)carbonyl]amino]-1-[4-(methylthio)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	533	413
	540.48	8-[(5-amino-2-chlorobenzoyl)amino]-1-[4-(methylthio)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$\leq 1 \mu\text{M}$	504	414

**[00248]** The compounds of Examples 415-420 in Table 20 were prepared by oxidation with *m*-CPBA with the appropriate sulfide.

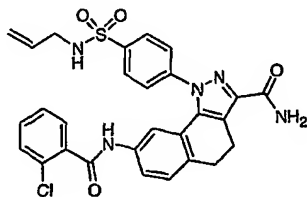
[00249] The bioactivity in the IKK2 Resin assay for the compounds of Examples 415-420 is shown in Table 20.

Table 20

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC <sub>50</sub>	MS (M+H)	Example
	444.54	1-[4-(methylsulfinyl)phenyl]-8-[(methylsulfonyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	445	415
	542.45	8-[(3-chloroisonicotinoyl)amino]-1-[4-(methylsulfinyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	≤ 1 μM	543	416
	549.01	8-[(6-chloro-1,3-benzodioxol-5-yl)carbonyl]amino-1-[4-(methylsulfinyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤ 1 μM	550	417
	556.48	8-[(5-amino-2-chlorobenzoyl)amino]-1-[4-(methylsulfinyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	≤ 1 μM	557	418
	505.00	8-[(2-chlorobenzoyl)amino]-1-[4-(methylsulfinyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤ 1 μM	505	419
	505.99	8-[(2-chloropyridin-3-yl)carbonyl]amino-1-[4-(methylsulfinyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤ 1 μM	506	420

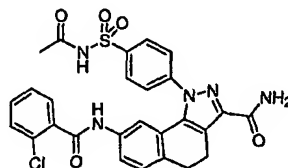
[00250] Example 421

1-{4-[(allylamino)sulfonyl]phenyl}-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

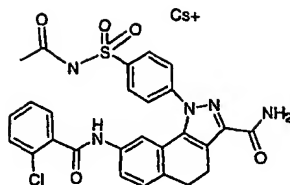


5

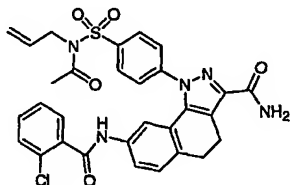
[00251] Step 1



- 10 To a stirring solution of 1-[4-(aminosulfonyl)phenyl]-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (2967 mg, 5.7 mmol) in THF (120 mL) was added DMAP (348 mg, 2.8 mmol), then tri-ethyl amine (0.95 mL, 6.8 mmol), followed by acetic anhydride (1.62 mL, 17.1 mmol). The reaction mixture was stirred at room temperature for overnight and then concentrated. To the residue
- 15 was added 5 % aq. NaHCO<sub>3</sub> (100 mL). All compounds were dissolved. The aq. Layer was washed with EA (100 mL x 2), CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The aq. layer was separated. To the aq. Layer was added 1N HCl to pH=6. A white precipitate was formed. It was filtered and washed with ether to give a white solid. The solid was dried under reduced pressure at 45°C to give 1-{4-[(acetylamino)sulfonyl]phenyl}-
- 20 8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (2255.4 mg, 70%).

**[00252]**      Step 2

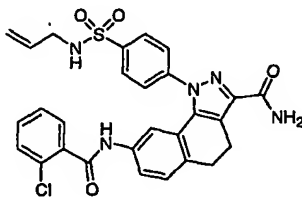
To a stirring solution of 1-(4-((acetylamino)sulfonyl)phenyl)-8-((2-chlorobenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (563 mg, 1 mmol) in H<sub>2</sub>O (5 mL) was added cesium carbonate (163 mg, 0.5 mmol). The suspension was stirred at room temperature for overnight. All compounds were dissolved. It was dried to give the Cs<sup>+</sup> salt (650 mg, 93 %).

**[00253]**      Step 3

10

To a stirring solution of the Cs<sup>+</sup> salt of 1-(4-((acetylamino)sulfonyl)phenyl)-8-((2-chlorobenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (637 mg, 0.92 mmol) in DMF (8 mL) was added a solution of allyl bromide (111 mg, 0.92 mmol). The solution was stirred at room temperature for over the weekend and concentrated. To the mixture was added MeOH- H<sub>2</sub>O (2:1). A precipitate was formed. It was filtered to give a yellow solid of 1-(4-((allylacetylamino)sulfonyl)phenyl)-8-((2-chlorobenzoyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (360 mg, 65%).

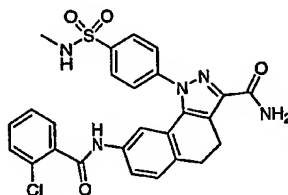
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**[00254]**      Step 4

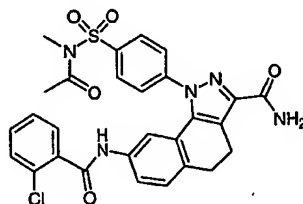
A solid of 1-(4-[[acetyl(allyl)amino]sulfonyl]phenyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (360 mg, 0.6 mmol) was dissolved in 0.5 N solution of NaOH in EtOH (10 mL) and stirred at room temperature for overnight. The mixture was concentrated. It was purified by HPLC to give the desired compound (210 mg, 62 %.) IKK-2 resin  $IC_{50} \leq 1 \mu M$ .

[00255] Example 422

8-[(2-chlorobenzoyl)amino]-1-{4-[(methylamino)sulfonyl]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

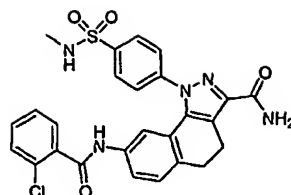


[00256] Step 1



To a stirring solution of 1-(4-[[acetyl(methyl)amino]sulfonyl]phenyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (563 mg, 1 mmol) in DMF (20 mL) was added  $NaH_2$  (40 mg, 1 mmol). The mixture was stirred at room temperature for 1 h. To the mixture was added a solution of Iodomethane (170.3 mg, 1.2 mmol) in DMF (1 mL). The solution was stirred at room temperature for 4 h and concentrated. It was purified by HPLC to give a solid of the desired compound 1-(4-[[acetyl(methyl)amino]sulfonyl]phenyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (155 mg, 27 %.)



[00257] Step 2

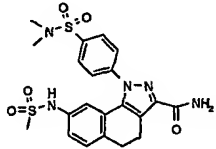
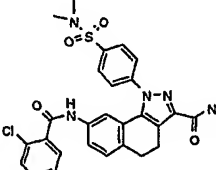
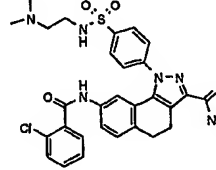
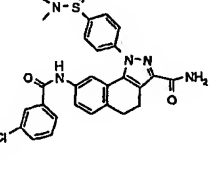
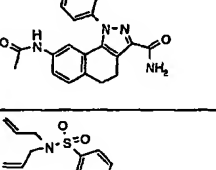
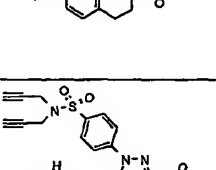
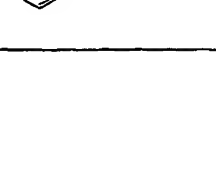
5 [00258] A solid of 1-(4-[[acetyl(methyl)amino]sulfonyl]phenyl)-8-[(2-chlorobenzoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide was dissolved in 0.5 N solution of NaOH in EtOH (3 mL) and stirred at room temperature for 2 h. A suspension was formed. It was filtered and washed to give the desired compound (29 mg, 53 %) IKK-2 resin IC<sub>50</sub> ≤ 1 μM.

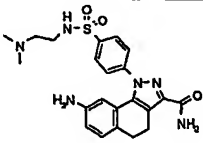
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[00259] The compounds of Examples 423-433 in Table 21 were prepared in a manner analogous to Example 46 using the appropriate alkylating agent and when appropriate acylating or sulfonating agent.

Table 21

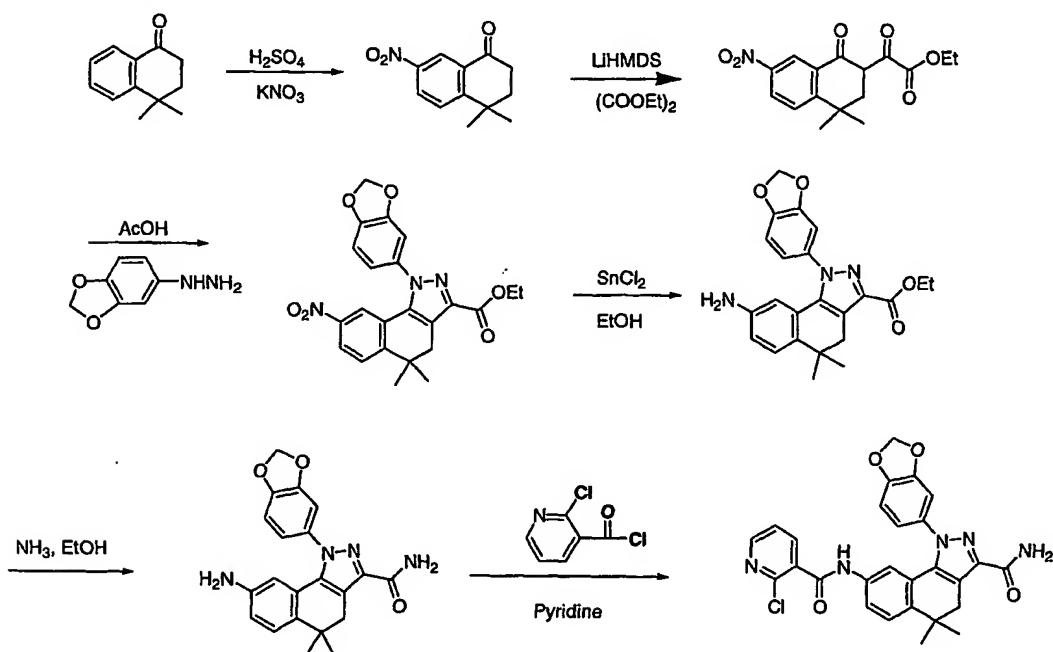
Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC <sub>50</sub>	MS (M+H)	Example
	435.51	8-amino-1-[4-(2,5-dihydro-1H-pyrrol-1-ylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	436	423
	453.52	8-amino-1-[4-(morpholin-4-ylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	454	424
	459.53	8-amino-1-[4-[(diprop-2-ynylamino)sulfonyl]phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤ 1 μM	460	425

Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	489.58	1-((4-((dimethylamino)sulfonyl)phenyl)-8-((methylsulfonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	490	426
	550.04	8-((2-chlorobenzoyl)amino)-1-((4-((dimethylamino)sulfonyl)phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	550	427
	593.11	8-((2-chlorobenzoyl)amino)-1-((4-((2-(dimethylamino)ethyl)amino)sulfonyl)phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	594	428
	550.04	8-((3-chlorobenzoyl)amino)-1-((4-((dimethylamino)sulfonyl)phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	550	429
	453.52	8-(acetamido)-1-((4-((dimethylamino)sulfonyl)phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	454	430
	541.65	1-((4-((diallylamino)sulfonyl)phenyl)-8-((methylsulfonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	542	431
	598.08	8-((2-chlorobenzoyl)amino)-1-((4-((diprop-2-ynylamino)sulfonyl)phenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	598	432

Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	454.56	8-amino-1-[(2-{[2-(dimethylamino)ethyl]amino}sulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$1 \leq 10 \mu\text{M}$	455	433

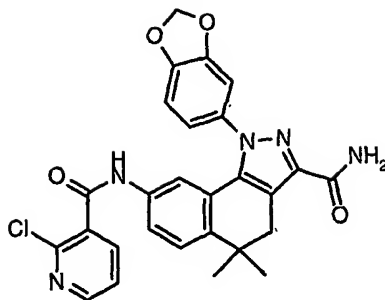
[00260] The following scheme was used for the synthesis of Examples 434

# SCHEME XXIX



[00261] Example 434

1-[(1,3-benzodioxol-5-yl)-8-[(2-chloropyridin-3-yl)carbonyl]amino]-5,5-dimethyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



[00262] Step 1

5 4,4-dimethyl-tetralone (6g) was suspended in 120ml conc.  $\text{H}_2\text{SO}_4$  at  $0^\circ\text{C}$ , then  $\text{KNO}_3$ (3.8g)/ $\text{H}_2\text{SO}_4$  (15ml) solution was added drop wise at  $0^\circ\text{C}$ . The reaction mixture was stirred at  $0^\circ\text{C}$  for three hours until the starting material was gone, then poured into about 100g of ice. After cooling down, the mixture was filtered, and the solid obtained was washed with water, hexane, and then dried under vacuum. 5.6g  
10 of desired product was obtained. It was used as it was without further purification. The structure was proved by LC-MS(220, M+1), HPLC,  $^1\text{H}$ NMR.

[00263] Step 2

15 The title compound of Step 1 (5.6g) was dissolved in 100ml THF, then  $(\text{COOEt})_2$  (5.6g) was added. The mixture was cooled down to  $-40^\circ\text{C}$ , and then, LiHMDS/1M THF solution (40ml) was added slowly. The reaction mixture was warmed up to r. t. slowly, then stirred overnight, and then neutralized with 2N aq. HCl. The mixture was extracted with EA (3x200ml). The EA solution was dried over  $\text{Na}_2\text{SO}_4$ . After  
20 filtration and evaporation of solvent, the residue was purified by HPLC (50% $\text{CH}_3\text{CN}$  to 90% $\text{CH}_3\text{CN}$  in 30 minutes). 1.3g of desired product was obtained. The structure was proved by LC-MS(320, M+1) and HPLC.

[00264] Step 3

25

The title compound of step 2 (1.3g) and 3,4-methylenedioxyphenylhydrazine hydrochloride ( 0.85g ) were suspended in 100 ml of HOAc. The mixture was heated up to reflux for 3 hours, and then the solvent was evaporated, and the residue was purified by HPLC (50% CH<sub>3</sub>CN/H<sub>2</sub>O to 90%CH<sub>3</sub>CN/H<sub>2</sub>O in 30 minutes). 0.65g of desired product was obtained and characterized by LC-MS(436, M+1), <sup>1</sup>HNMR, HPLC analysis.

[00265] Step 4

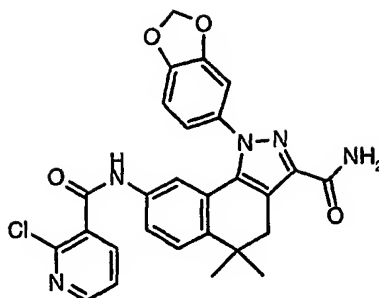
The title compound of step 3 (0.65g) was suspended in 100ml of EtOH, and then SnCl<sub>2</sub> (1.2g) were added. The reaction mixture was refluxed overnight. Then the solvent was evaporated, and residue was dissolved in 15ml CH<sub>3</sub>CN and filtered. The solution was purified by HPLC (40% CH<sub>3</sub>CN/H<sub>2</sub>O to 90% CH<sub>3</sub>CN/H<sub>2</sub>O in 30 minutes). 0.25g of desired product was obtained and characterized by HPLC and LC-MS(406, M+1).

[00266] Step 5

The title compound of step 4 (0.25g) was dissolved in EtOH and liquid ammonia, and heated up to 100C under 600 PSI for 36 hours. After releasing pressure and evaporating solvent, the residue is purified by HPLC (5% CH<sub>3</sub>CN/H<sub>2</sub>O to 60% CH<sub>3</sub>CN/H<sub>2</sub>O in 30 minutes). 200mg of desired product was obtained, and characterized by LC-MS(376, M+1) and HPLC analysis.

[00267] Step 6

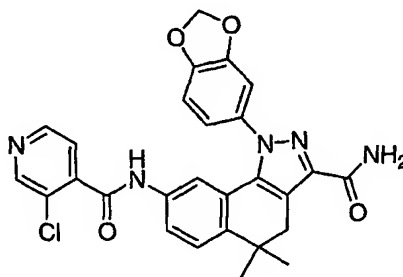
The title compound of step 5 ( 90mg) was dissolved in pyridine(5ml), then 2-chloro-nictinoyl chloride (52mg) were added. The reaction mixture was stirred overnight, and then solvent was evaporated. The residue was purified by HPLC(30% CH<sub>3</sub>CN/H<sub>2</sub>O to 90%CH<sub>3</sub>CN/H<sub>2</sub>O in 30 minutes) 49 mg of desired compound 1-(1,3-benzodioxol-5-yl)-8-{[(2-chloropyridin-3-yl)carbonyl]amino}-5,5-dimethyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



The resulting compound was obtained and analyzed by <sup>1</sup>HNMR, LC-MS(516, M+1), HPLC and CHN analysis.

5 [00268] Example 435

1-(1,3-benzodioxol-5-yl)-8-[(3-chloroisonicotinoyl)amino]-5,5-dimethyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



10

The tile compound of Example 332 (90mg) was dissolved in 5ml DMF, then 2-chloroisonicotinic acid(100mg), HATU(150mg) and diisopropylethylamine(0.5ml) were added. The reaction mixture was stirred at r. t. for two days. After the reaction was complete, solvent was evaporated, and the residue was purified by HPLC(30% CH<sub>3</sub>CN/H<sub>2</sub>O to 90% CH<sub>3</sub>CN/H<sub>2</sub>O in 30 minutes). 100mg of product was obtained and characterized by <sup>1</sup>HNMR, LC-MS (516, M+1), HPLC, CHN analysis.

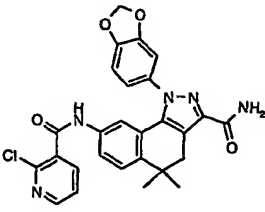
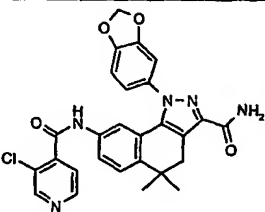
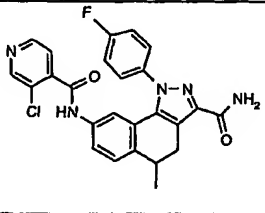
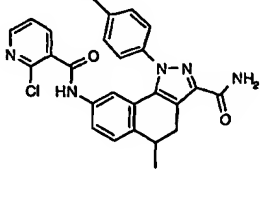
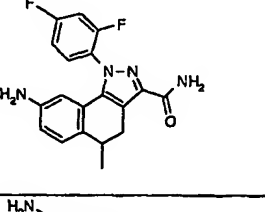
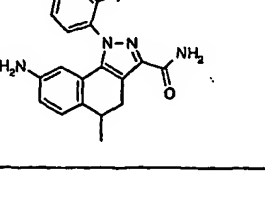
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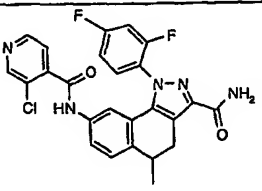
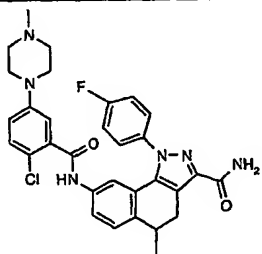
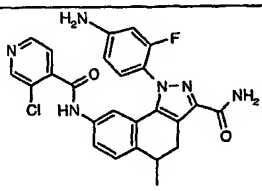
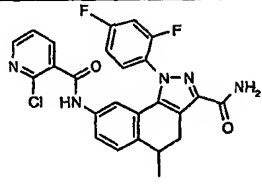
[00269] The compounds of Examples 436-443 in Table 22 were prepared in a manner analogous to Examples 434 and 435

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[00270] The bioactivity in the IKK2 Resin assay for the compounds of Examples 434-443 is shown in Table 22.

Table 22

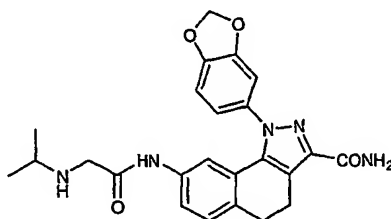
Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	515.96	1-((2-chloropyridin-3-yl)carbonyl)-5,5-dimethyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	516	434
	515.96	1-((3-chloroisonicotinoyl)amino)-5,5-dimethyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	552	435
	475.91	8-((3-chloroisonicotinoyl)amino)-1-(4-fluorophenyl)-5-methyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	476	436
	475.91	8-(((2-chloropyridin-3-yl)carbonyl)amino)-1-(4-fluorophenyl)-5-methyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	476	437
	354.36	8-amino-1-(2,4-difluorophenyl)-5-methyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	nd	355	438
	351.39	8-amino-1-(4-amino-2-fluorophenyl)-5-methyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	nd	352	439

Compound No., Structure	Mol. Wt.	Compound Name	IKK2 Resin IC50	MS (M+H)	Example
	493.90	8-[(3-chloroisonicotinoyl)amino]-1-(2,4-difluorophenyl)-5-methyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	494	440
	573.08	8-[[2-chloro-5-(4-methylpiperazin-1-yl)benzoyl]amino]-1-(4-fluorophenyl)-5-methyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	574	441
	490.93	1-(4-amino-2-fluorophenyl)-8-[(3-chloroisonicotinoyl)amino]-5-methyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	491	442
	493.90	8-[[2-chloropyridin-3-yl]carbonyl]amino]-1-(2,4-difluorophenyl)-5-methyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	nd	494	443

nd = not determined

[00271] Example 444

- 5 1-(1,3-benzodioxol-5-yl)-8-[(N-isopropylglycyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide





**[00272]** Step 1

To a solution of 8-amino-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (1.00 g, 2.87mmol) in DMA (5.0 mL) was added chloroacetyl chloride (0.27 mL, 3.44 mmol) and triethylamine (0.48 mL, 3.44 mmol) and the mixture was stirred at RT overnight. The reaction mixture was trituated with distilled water (3x40 mL) and the solid product precipitated out once the water was added. The mixture was filtered and the solid was dried under the vacuum oven overnight to give 8-[(chloroacetyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide. MS (ESI+) for C<sub>21</sub>H<sub>17</sub>ClN<sub>4</sub>O<sub>4</sub> *m/z* 425 (M+H)<sup>+</sup>.

**[00273]** Step 2

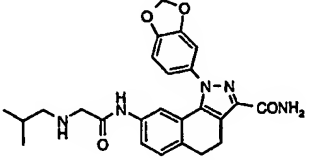
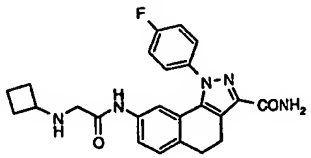
To a solution of product from step 1 (0.10 g, 0.24 mmol) dissolved in DMA (2.0 mL) was added isopropyl amine (3.0 eq) followed by the PS-DIEA resin (2.0 eq). The mixture was stirred and heated at 100 °C overnight. The reaction mixture was cooled to RT and the solution was filtered. The filtrate was then evaporated under a stream of nitrogen overnight. The sample was purified on the SPE silica column. The clean fractions were combined and concentrated to give the title material. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.38 (dd, 1H), 7.28 (d, 1H), 7.18 (d, 1H), 7.0 (t, 1H), 6.96 (d, 2H), 6.12 (s, 2H), 3.29 (s, 2H), 3.04 (m, 2H), 2.95 (m, 2H), 2.79 (m, 1H), 1.08 (d, 6H); MS (ESI+) for C<sub>24</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub> *m/z* 448 (M+H)<sup>+</sup>.

**[00274]** The compounds of Examples 445-452 listed in the table below where prepared according to the procedure of Example 444 using the appropriately substituted aniline and appropriate amine.

**[00275]** The bioactivity in the IKK2 Resin assay for the compounds of Examples 444-452 is shown in Table 23

Table 23

Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	LCMS (M+H)	Example
	447.50	1-(1,3-benzodioxol-5-yl)-8-[(N-isopropylglycyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	448	444
	495.97	1-(1,3-benzodioxol-5-yl)-8-[(N-cyclobutylglycyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$\leq 1 \mu\text{M}$	460	445
	495.97	1-(1,3-benzodioxol-5-yl)-8-[(pyrrolidin-1-ylacetyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$1 \leq 10 \mu\text{M}$	460	446
	524.02	1-(1,3-benzodioxol-5-yl)-8-[(N-cyclohexylglycyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$1 \leq 10 \mu\text{M}$	488	447
	455.91	1-(1,3-benzodioxol-5-yl)-8-[(N-methylglycyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$1 \leq 10 \mu\text{M}$	420	448
	495.97	1-(1,3-benzodioxol-5-yl)-8-[(N-(cyclopropylmethyl)glycyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride	$1 \leq 10 \mu\text{M}$	460	449
	461.53	1-(1,3-benzodioxol-5-yl)-8-[(N-(tert-butyl)glycyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	462	450

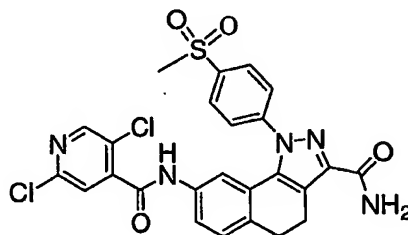
Compound No., Structure	Mol. Wt.	Compound Name(s)	IKK2 Resin IC50	LCMS (M+H)	Example
	461.53	1-(1,3-benzodioxol-5-yl)-8-[(N-isobutylglycyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	462	451
	433.49	8-[(N-cyclobutylglycyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	434	452

## Example 453

8-{[(5-Chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

## Step 1

8-[(2,5-Dichloroisonicotinoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

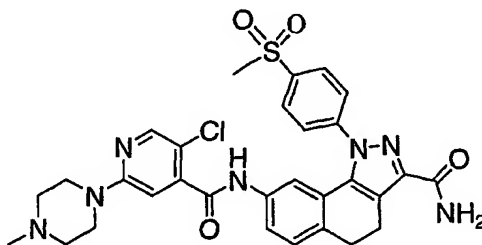


[00276] The product of Example 92 (8-amino-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide hydrochloride) (1.20 mmol), 2,5-dichloroisonicotinic acid (1.83 mmol), HATU (1.83 mmol), and 0.7 mL triethylamine were dissolved in 10 mL DMF. The mixture was stirred at r.t. overnight before more triethylamine (0.4 mL), HATU (1.29 mmol), and 2,5-dichloroisonicotinic (2.24 mmol) were added to drive the reaction. After another 2.5 h, the mixture was added to water, causing a precipitate, which was filtered and washed with water. After trituration in water, the product was dissolved in

tetrahydrofuran, decolorized with activated carbon, dried over  $\text{MgSO}_4$ , and the solvent stripped. The solid was dissolved in anhydrous acetonitrile, filtered, and the acetonitrile stripped. The residue was purified by recrystallizations from absolute ethanol followed by triturations with anhydrous acetonitrile. Mp: 215-222°C. Mass spectrum:  $M + 1 = 556$ .  $^1\text{H}$  NMR ( $\delta$ ,  $d_6$ -DMSO, 400 MHz): 2.87-2.98 (m, 4H); 3.18 (s, 3H); 7.29-7.38 (m, 4H); 7.60 (s, 1H); 7.76 (s, 1H); 7.80-7.85 (m, 2H); 8.06-8.11 (m, 2H); 8.58 (s, 1H); 10.56 (s, 1H).

## Step 2

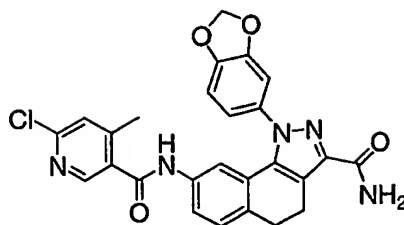
8-[[5-Chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



[00277] The product of step 1 (0.92 mmol) and N-methylpiperazine (9.0 mmol) were combined with 2.6 mL DMA. The reaction mixture was placed under nitrogen and stirred in an oil bath at 100°C for 15 h. The mixture was then added to water, causing a precipitate, which was filtered and washed with water. The solid was dissolved in acetonitrile, dried over  $\text{MgSO}_4$ , and the solvent stripped. Mass spectrum:  $M + 1 = 620$ .

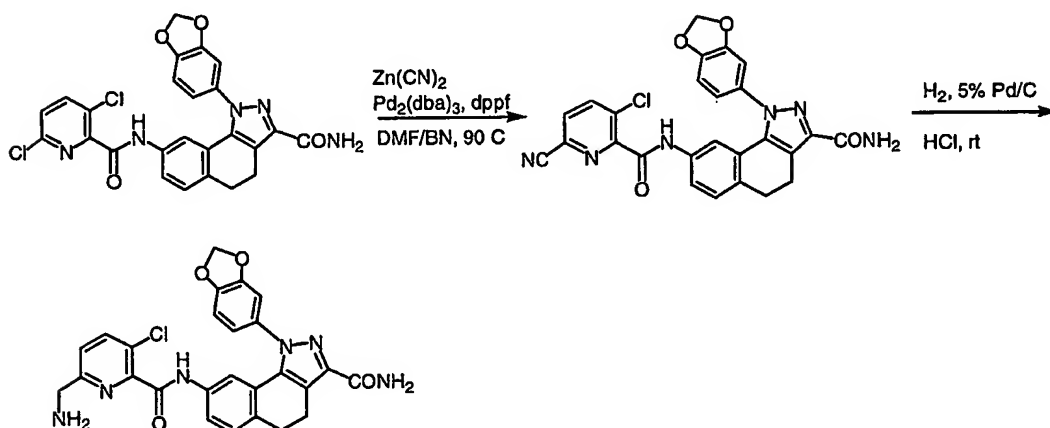
## Example 454

1-(1,3-Benzodioxol-5-yl)-8-[[[(6-chloro-4-methylpyridin-3-yl)carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



[00278] The product of Example 161, Step 4 (5.93 mmol), 6-chloro-4-methylnicotinic acid (Example 246, Step 1) (8.91 mmol), HATU (8.73 mmol), and 3.0 mL triethylamine were dissolved in 30 mL DMF. The mixture was stirred at r.t. for 5.4 h. The solvent was then partially stripped and the residue suspended in water, filtered, and washed with water. The solid was dissolved in tetrahydrofuran, decolorized with activated carbon, dried over  $\text{MgSO}_4$ , and the solvent stripped. The product was purified by recrystallizations in tetrahydrofuran and a trituration in ethanol/water. Mp:  $303^\circ\text{C}$  (decomp.). Mass spectrum:  $M + 1 = 502$ .  $^1\text{H}$  NMR ( $\delta$ ,  $d_6$ -DMSO, 400 MHz): 2.28 (s, 3H); 2.81-2.96 (m, 4H); 6.06 (s, 2H); 6.90-6.94 (m, 1H); 6.97-7.01 (m, 1H); 7.08 (d, 1H,  $J = 2.0$  Hz); 7.20-7.39 (m, 4H); 7.45-7.49 (m, 2H); 8.34 (s, 1H); 10.30 (s, 1H)

[00279] Examples 455, 456, and 457 were synthesized by the following general synthesis procedure, illustrated for Example 455:

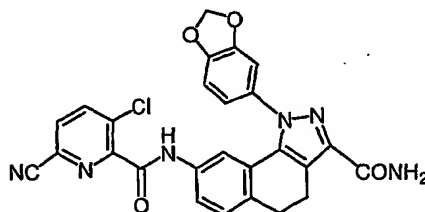


## Example 455

[00280] 8-({[6-(Aminomethyl)-3-chloropyridin-2-yl]carbonyl}amino)-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

## 5 Step 1

1-(1,3-Benzodioxol-5-yl)-8-{{[(3-chloro-6-cyanopyridin-2-yl)carbonyl]amino}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



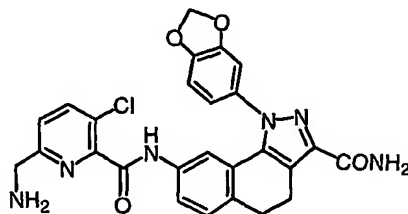
10

[00281] The product of Example 216 (1-(1,3-benzodioxol-5-yl)-8-{{[(3,6-dichloropyridin-2-yl)carbonyl]amino}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (1.045 g, 2 mmol), Zn(CN)<sub>2</sub> (0.138 g, 1.2 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.0904 g, 0.1 mmol) (dba = dibenzylideneacetone), and dppf (dppf =

15 bis[diphenylphosphino]ferrocene) (0.121 g, 0.22 mmol) were mixed in a flask containing stir bar. The mixture was placed under vacuum then nitrogen three times to remove oxygen. Degassed anhydrous solvents (9 mL of DMF and 3 mL of benzonitrile) were added under N<sub>2</sub>, and the flask was placed in an oil bath at 90 C for 6 h. After 6 h solvent was removed under vacuum, 50 mL of ether was added  
20 and stirred 3 h. Ether was removed by filtration, and the solid was triturated with 50 mL of water 3 h, dried and purified by HPLC. The title compound is a yellow solid (0.234 g, 23%). <sup>1</sup>H NMR (d<sub>6</sub>-DMSO): δ 2.82-3.01 (m, 4H), 6.09 (s, 2H), 6.97-7.07 (m, 2H), 7.14 (d, 1H, J = 3 Hz), 7.27 (s, 1H), 7.33-7.40 (m, 3H), 7.52 (s, 1H), 8.21 (d, 1H, J = 8 Hz), 8.39 (d, 1H, J = 8 Hz), 10.60 (s, 1H). ESI mass  
25 spectrum for C<sub>26</sub>H<sub>18</sub>ClN<sub>6</sub>O<sub>4</sub><sup>+</sup>: 513 (M + 1).

## Step 2

8-([6-(Aminomethyl)-3-chloropyridin-2-yl]carbonyl)amino)-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



5

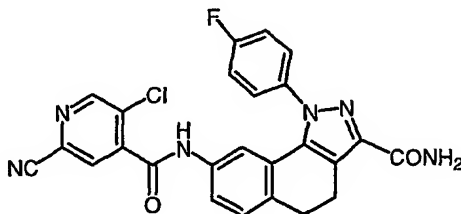
[00282] The product of step 1 (0.24 g, 0.47 mmol) was dissolved in a mixture of anhydrous solvents, containing glyme (3 mL), methanol (9 mL), and 1.2 M solution of HCl in methanol (3 mL). The mixture was placed under N<sub>2</sub>, in Fisher-Potter bottle, containing magnetic stir bar and 0.02g of 5% Pd/C catalyst (Degussa -  
 10 Frankfurt, Germany). Previously, the catalyst was dried and preactivated (H<sub>2</sub>, 50 psi, 30 minutes). The hydrogenation was carried out under 3 psi pressure for 3 hours at room temperature. The catalyst was removed by filtration, and the filtrate was purified by HPLC to give 0.152 g of TFA salt of 8-([6-(Aminomethyl)-3-chloropyridin-2-yl]carbonyl)amino)-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-  
 15 benzo[g]indazole-3-carboxamide, which was triturated in water-triethyl amine mixture (2:1) for 30 minutes. The title compound (0.12 g, 49%) was obtained as the free base (a white solid) after filtration and drying. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO): δ 2.03 (s, 2H), 2.82-3.00 (m, 4H), 3.80 (s, 2H), 6.09 (s, 2H), 6.92-7.03 (m, 2H), 7.15 (d, 1H, J = 2 Hz), 7.25 (s, 1H), 7.28-7.44 (m, 3H), 7.49 (s, 1H), 7.58 (d, 1H, J = 8.5  
 20 Hz), 7.96 (d, 1H, J = 8.5 Hz), 10.40 (s, 1H). ESI mass spectrum for C<sub>26</sub>H<sub>22</sub>ClN<sub>6</sub>O<sub>4</sub><sup>+</sup>: 517 (M + 1).

#### Example 456

8-{[2-(Aminomethyl)-5-chloroisonicotinoyl]amino}-1-(4-fluorophenyl)-4,5-  
 25 dihydro-1H-benzo[g]indazole-3-carboxamide

#### Step 1

8-[(5-Chloro-2-cyanoisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



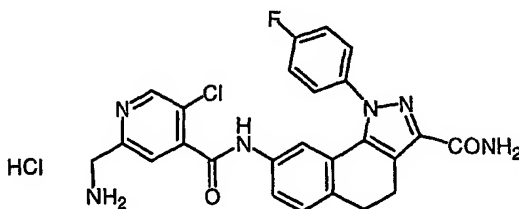
5

[00283] The compound of step 1 was synthesized by the same procedure as in step 1 of Example 455 for 1-(1,3-Benzodioxol-5-yl)-8-[[3-chloro-6-cyanopyridin-2-yl]carbonyl]amino}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide starting with the compound of Example 248 (8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (1.67 g, 3.2 mmol), Zn(CN)<sub>2</sub> (0.230 g, 2 mmol), Pd<sub>2</sub>(DBA)<sub>3</sub> (0.203 g, 0.22 mmol), and DPPF (0.121 g, 0.52 mmol), in a mixture of DMF (6 mL) and benzonitrile (2 mL). The mixture was heated at 90°C for 6 h. Solvents were removed under reduced pressure. The residue was triturated with 50 mL of ether overnight and filtered to give 2.2 g of a brown solid. The title compound, isolated from 0.8 g of the crude reaction mixture by preparative HPLC, is a white solid (0.30 g), M.p. 275-276°C. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 2.94 - 3.17 (m, 4H), 7.20-7.48 (m, 9H), 8.01 (s, 1H), 8.82 (s, 1H). ESI mass spectrum for C<sub>25</sub>H<sub>17</sub>ClFN<sub>6</sub>O<sub>2</sub><sup>+</sup>: 487 (M + 1).

20

## Step 2

8-[[2-(Aminomethyl)-5-chloroisonicotinoyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



25



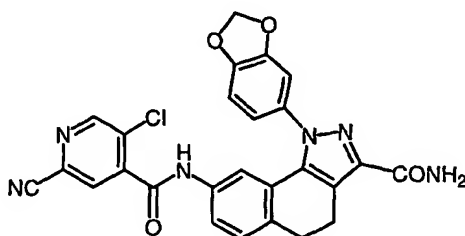
[00284] The title compound was synthesized by the same procedure as in step 2 of Example 455 for 8-({[6-(Aminomethyl)-3-chloropyridin-2-yl]carbonyl}amino)-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide starting with 1.2 g of the crude reaction mixture containing the compound of step 1 and 0.4 g of 10% Pd/C (Aldrich) in a mixture of glyme (3 mL), methanol (14 mL), and 1.2 M solution of HCl in methanol (6 mL). The hydrogenation was carried out under 5 psi pressure for 8 h at room temperature. The catalyst was removed by filtration, and the filtrate was purified by HPLC to give 0.43 g of the TFA salt of 8-([2-(Aminomethyl)-5-chloroisonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide, which was triturated in 2N HCl for 3 hours. The title compound (0.35 g) as the HCl salt (white solid) was obtained after filtration and drying. M.p., 312-314°C. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 2.91 - 3.15 (m, 4H), 4.33 (s, 2H), 6.09 (s, 2H), 7.22 - 7.42 (m, 5H), 7.38 - 7.52 (m, 3H), 8.78 (s, 1H). ESI mass spectrum for C<sub>25</sub>H<sub>21</sub>ClFN<sub>6</sub>O<sub>2</sub><sup>+</sup>: 491 (M + 1).

#### Example 457

8-([2-(Aminomethyl)-5-chloroisonicotinoyl]amino)-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

#### Step 1

1-(1,3-Benzodioxol-5-yl)-8-[(5-chloro-2-cyanoisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

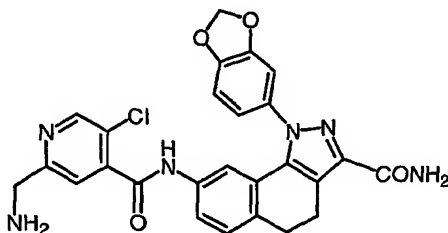


[00285] The compound of step 1 was synthesized by the same procedure as in step 1 of Example 455 for 1-(1,3-Benzodioxol-5-yl)-8-([3-chloro-6-cyanopyridin-2-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-

carboxamide starting with the compound of Example 211 (1-(1,3-benzodioxol-5-yl)-8-[(2,5-dichloroisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (2.16 g, 4.1 mmol), Zn(CN)<sub>2</sub> (0.287 g, 2.5 mmol), Pd<sub>2</sub>(DBA)<sub>3</sub> (0.203 g, 0.24 mmol), and DPPF (0.121 g, 0.55 mmol), in a mixture of DMF (9 mL) and benzonitrile (3 mL). The mixture was heated at 90°C for 6 hours. Solvents were removed under reduced pressure. The residue was triturated with 50 mL of ether overnight and filtered to give 2.8 g a brown solid. The product, isolated from 0.9 g of the crude reaction mixture by preparative HPLC, is a white solid (0.35 g), M.p. 321-322°C. <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO): δ 2.82-3.01 (m, 4H), 6.10 (s, 2H), 6.94-7.06 (m, 2H), 7.11 (d, 1H, J = 2 Hz), 7.24-7.38 (m, 4H), 7.52 (s, 1H), 8.38 (s, 1H), 8.97 (s, 1H). ESI mass spectrum for C<sub>26</sub>H<sub>18</sub>ClN<sub>6</sub>O<sub>4</sub><sup>+</sup>: 513 (M + 1).

#### Step 2

8-{[2-(Aminomethyl)-5-chloroisonicotinoyl]amino}-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



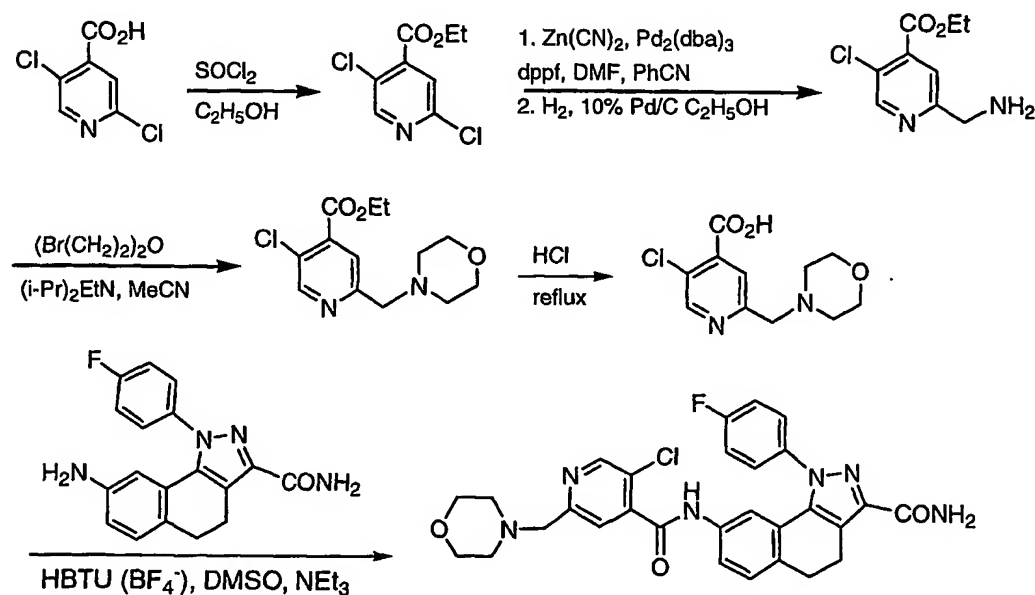
[00286] The title compound was synthesized by the same procedure as in step 2 of Example 455 for 8-([6-(Aminomethyl)-3-chloropyridin-2-yl]carbonyl)amino)-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide starting with 1.4 g of the crude reaction mixture containing the compound of step 1 and 0.6 g of 10% Pd/C (Aldrich) in a mixture of glyme (20 mL), methanol (30 mL), and 1.2 M solution of HCl in methanol (10 mL). The hydrogenation was carried out under 5 psi pressure for 8 h at room temperature. The catalyst was removed by filtration, and the filtrate was purified by HPLC to give 0.52 g of TFA salt of the title compound, which was triturated in 1N HCl (2:1) for 3 h. The title compound (0.40

g) as the HCl salt (a white solid) was obtained after filtration and drying. M.p., 125-130°C. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 2.90 -3.16 (m, 4H), 4.34 (s, 2H), 6.09 (s, 2H), 6.92 - 7.03 (m, 3H), 7.38(s, 2H), 7.40 (s, 1H), 7.57 (s, 1H), 8.78 (s, 1H). ESI mass spectrum for C<sub>26</sub>H<sub>23</sub>ClN<sub>6</sub>O<sub>4</sub><sup>+</sup>: 518 (M + 1).

5

[00287] Examples 458 and 459 were synthesized by the following synthesis procedure, illustrated for Example 458.

## SCHEME XXX



10

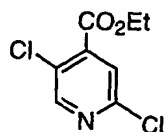
## Example 458

8-([3-Chloro-6-(morpholin-4-ylmethyl)pyridin-2-yl]carbonyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

15

## Step 1

Ethyl 2,5-dichloroisonicotinate



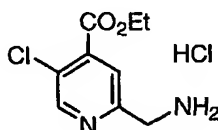
20

[00288] 2,5-Dichloroisonicotinic acid (7.2 g, 37.5 mmol) and 180 mL of anhydrous  $C_2H_5OH$  were placed in a flask containing magnetic stir bar under  $N_2$ . The mixture was cooled to  $0^\circ C$  and 5.6 mL of  $SOCl_2$  (38 mmol) was added dropwise. The solution was heated under reflux overnight. Volatiles were partially  
5 evaporated to decrease the volume to 30 mL. The residue was partitioned between a water solution of  $Na_2CO_3$  with pH = 8.5 (75 mL) and  $CH_2Cl_2$  (75 mL). The organic layer was separated. The aqueous layer was extracted with  $CH_2Cl_2$  (2 x 25 mL). The organic layers were combined, dried over  $MgSO_4$ , and concentrated in vacuo to give 7.8 g of product (97.5% yield).  $^1H$  NMR ( $DCCl_3$ ):  $\delta$  1.42 (t, 3H, J = 7  
10 Hz), 4.44 (q, 2H, J = 7 Hz), 7.68 (s, 1H), 8.50 (s, 1H). ESI mass spectrum for  $C_8H_8Cl_2NO_2^+$ : 220 (M + 1).

#### Step 2

Ethyl 2-(aminomethyl)-5-chloroisonicotinate hydrochloride

15



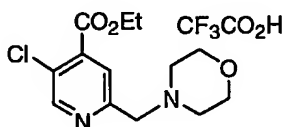
[00289] All dried reagents (7.8 g (35.45 mmol) of ethyl 2,5-dichloroisonicotinate, 4.5 g (3.5 mmol) of  $Zn(CN)_2$ , 0.226 g (0.41 mmol) of dppf  
20 (dppf = bis[diphenylphosphino]ferrocene), and 0.170 g (0.19 mmol) of  $Pd_2(dba)_3$  (dba = dibenzylideneacetone) were mixed in a flask containing a stir bar. Degassed anhydrous solvents (10 mL of DMF and 3.3 mL of benzonitrile) were added under  $N_2$ , and the flask was placed in an oil bath at  $90^\circ C$  for 6 h. After 6 h solvents were removed under vacuum, then 100 mL of water was added and the residue was  
25 triturated for 3 h. After filtration, the solid was dried under reduced pressure to give about 7 g of product mixture, which was used for reduction without further purification. Both starting material and ethyl dicyanoisonicotinate were detected.

[00290] This product mixture (7 g) was placed in a Fisher-Porter bottle with  
30 1.8 g of 10% Pd/C (Aldrich) in 120 mL of EtOH and 30 mL of  $Et_2O-HCl$  (2M

solution) under a hydrogen atmosphere (2-3 psi) and stirred at RT for 3 hours. After removing solvent, the oil was triturated with ether to give a brownish solid, which, after filtration, was triturated with 10 mL of CH<sub>3</sub>CN to give 4.2 g of the title compound as the HCl salt (47% yield). <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.41 (t, 3H, J = 7 Hz), 4.38 (s, 2H), 4.46 (q, 2H, J = 7 Hz), 7.80 (s, 1H), 8.78 (s, 1H). ESI mass spectrum for C<sub>9</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup>: 215 (M + 1).

### Step 3

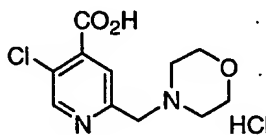
Ethyl 5-chloro-2-(morpholin-4-ylmethyl)isonicotinate trifluoroacetate



[00291] The product from step 2 (1.77 g, 7 mmol), 2-bromoethyl ether (2.18 g, 9.5 mmol), and ethyldiisopropylamine (2.5 g, 19 mmol) in 10 mL of acetonitrile were placed in a flask containing magnetic stir bar. The reaction mixture was stirred for 8 days at room temperature. Volatiles were removed under reduced pressure, and the desired product (solid, 1.3 g, 65% yield) was isolated with preparative HPLC as the TFA salt. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.42 (t, 3H, J = 7 Hz), 3.41 (s, broad, 4H), 4.46 (q, 2H, J = 7 Hz), 4.58 (s, 2H), 4.88 (s, broad, 4H), 7.90 (s, 1H), 8.83 (s, 1H). ESI mass spectrum for C<sub>13</sub>H<sub>18</sub>ClN<sub>2</sub>O<sub>3</sub><sup>+</sup>: 285 (M + 1).

### Step 4

5-Chloro-2-(morpholin-4-ylmethyl)isonicotinic acid hydrochloride



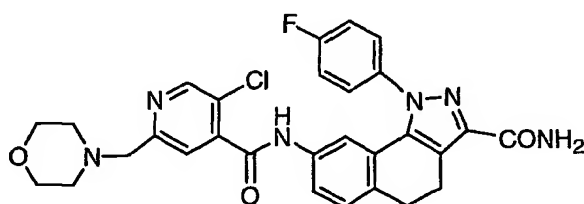
[00292] The compound of step 3 (2.69 g, 10.3 mmol) as a suspension in 3N HCl (15 mL) was heated under reflux for 3 hours. Volatiles were removed under

reduced pressure to give 1.88 g (95% yield) of the title compound.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  3.30 (s, broad, 2H), 3.41 (s, broad, 2H), 3.83 (s, broad, 2H), 4.05 (s, broad, 2H), 4.58 (s, 2H), 7.92 (s, 1H), 8.83 (s, 1H). ESI mass spectrum for  $\text{C}_{11}\text{H}_{14}\text{ClN}_2\text{O}_3^+$ : 257 ( $M + 1$ ).

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#### Step 5

8-([3-Chloro-6-(morpholin-4-ylmethyl)pyridin-2-yl]carbonyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamid.



10

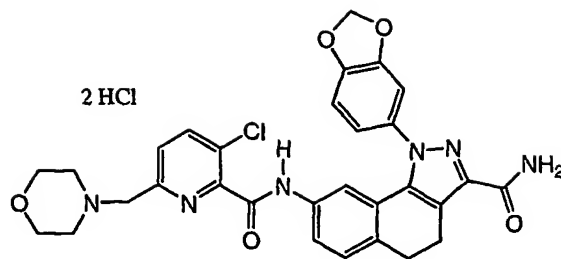
**[00293]** The title compound was synthesized from 0.94 g (3.2 mmol) of 5-chloro-2-(morpholin-4-ylmethyl)isonicotinic acid hydrochloride (step 4) and the compound of Example 244 (8-amino-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (0.69 g, 2.1 mmol) by the same procedure used for Example 255 except that DMF was replaced with DMSO (4 mL). The title compound is a brownish solid (0.31 g, 26%), M.p., 310-315° C (decomp.).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  2.78 - 2.82 (m, 4H), 2.92 - 3.12 (m, 4H), 3.76 - 3.80 (m, 4H), 3.98 (s, 2H), 7.21 - 7.42 (m, 5H), 7.50 - 7.63 (m, 3H), 8.63 (s, 1H). ESI mass spectrum for  $\text{C}_{29}\text{H}_{27}\text{ClFN}_6\text{O}_3^+$ : 561 ( $M + 1$ ).

20

#### Example 459

1-(1,3-Benzodioxol-5-yl)-8-([3-chloro-6-(morpholin-4-ylmethyl)pyridin-2-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

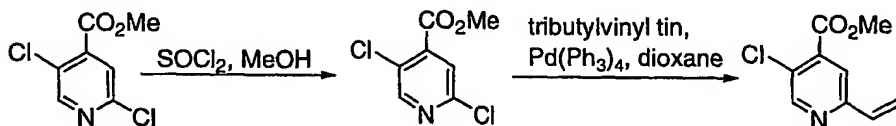
25



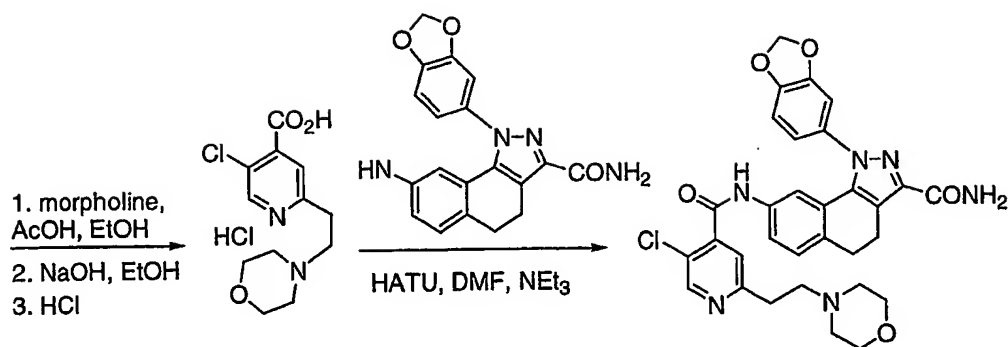
[00294] The title compound was synthesized from 1.0 g (3.4 mmol) of 5-chloro-2-(morpholin-4-ylmethyl)isonicotinic acid hydrochloride (step 4 of Example 458) and the product of Example 161, Step 3 (0.78 g, 2.2 mmol) by the same procedure used for Example 255 except that DMF was replaced with DMSO (5 mL). The title compound was initially isolated as the TFA salt by preparative HPLC. After trituration with 2N HCl (2 x 20 mL) it was filtered and dried under reduced pressure to give the product as the bis(hydrochloride) tetrahydrate (0.35 g, 22% yield), M.p., 231-235° C (decomp.). <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 2.50 - 2.54 (m, 4H), 2.92 - 3.12 (m, 4H), 3.76 - 3.80 (m, 6H), 6.09 (s, 2H), 6.90 - 7.10 (m, 3H), 7.38 - 7.42 (m, 3H), 7.58 (s, 1H), 8.60 (s, 1H). ESI mass spectrum for C<sub>30</sub>H<sub>28</sub>ClN<sub>6</sub>O<sub>5</sub><sup>+</sup>: 587 (M + 1).

Examples 460 and 461 were synthesized by the following synthesis procedure, illustrated for the synthesis of Example 461.

#### SCHEME XXXI



20

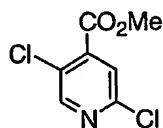


## Example 460

1-(1,3-Benzodioxol-5-yl)-8-{{[5-chloro-2-(2-morpholin-4-ylethyl)isonicotinoyl]amino}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

## Step 1

Methyl 2,5-dichloroisonicotinate



10

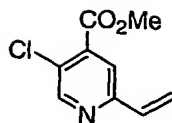
[00295] Thionyl chloride (9.13 g, 5.6 mL, 76 mmol) was added at 0°C to a suspension of 2,5-dichloroisonicotinic acid (7.3 g, 38 mmol) in 170 mL of MeOH. The reaction mixture was refluxed overnight. The volatiles were evaporated and the resulting residue was basified (pH = 9) with a saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extract was dried over MgSO<sub>4</sub>. Purification by chromatography on silica gel (hexanes / EtOAc : 4/1) afforded the title compound as a white solid, yield 89%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.98 (s, 3H), 7.7 (s, 1H), 8.49 (s, 1H), <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): δ 53.4, 125.2, 129.2, 139.3, 150.1, 151.1, 163.4. Mass spectrum, M + 1 = 207.

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## Step 2

Methyl 2-vinyl-5-chloroisonicotinate

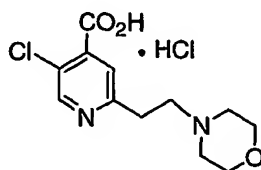




[00296] Pd(PPh<sub>3</sub>)<sub>4</sub> (263 mg, 0.6 %) was added to a degassed mixture of methyl 2,5-dichloroisonicotinate (step 1) (8.39 g, 40.7 mmol) and tributyl(vinyl)tin (15.4 g, 14.24 mL, 48.5 mmol) in 100 mL THF. The reaction mixture was stirred at 60°C for 4 days. The solvent was evaporated and the resulting residue partitioned between CH<sub>2</sub>Cl<sub>2</sub> and a saturated aqueous solution of KF. The CH<sub>2</sub>Cl<sub>2</sub> extract was washed with H<sub>2</sub>O and dried over MgSO<sub>4</sub>. Purification by chromatography on silica gel (hexanes / EtOAc : 20/1 to 10/1) afforded the title compound as a colorless oil, yield 74 %. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.96 (s, 3H), 5.55 (d, 1H, *J*<sub>cis</sub> = 10.8 Hz), 6.24 (d, 1H, *J*<sub>trans</sub> = 17.5 Hz), 6.78 (dd, 1H, *J*<sub>trans</sub> = 17.5 Hz, *J*<sub>cis</sub> = 10.8 Hz), 7.65 (s, 1H), 8.62 (s, 1H), <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): δ 53.2, 120.2, 121.9, 128.6, 135.3, 137.2, 151.1, 154.7, 164.8. <sup>1</sup>H-<sup>13</sup>C and <sup>1</sup>H-<sup>15</sup>N correlation spectroscopy (ghmhc) confirmed the structure.

### Step 3

#### 2-(Morpholin-4-ylethyl)-5-chloroisonicotinic acid hydrochloride



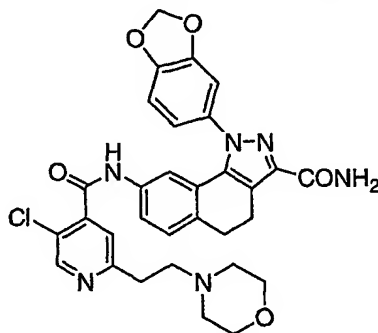
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[00297] A mixture of the material from step 2 (1.5 g, 7.5 mmol), morpholine (0.97 g, 0.97 mL, 11 mmol) and acetic acid (0.66 g, 0.63 mL, 11 mmol) in 7 mL EtOH was refluxed for 2 days. The reaction mixture was concentrated under vacuum and the resulting residue basified to pH = 8 to 9 with a saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were dried over MgSO<sub>4</sub>. The crude product, consisting of a mixture of methyl and ethyl 5-chloro-2-(morpholinoethyl)-isonicotinic esters, and was stirred with NaOH (1 mol/L, 7.5 mL, 7.5 mmol) in 20 mL of EtOH, at room temperature for 2 h. The

volatiles were removed and the basic aqueous residue washed once with  $\text{CH}_2\text{Cl}_2$ . The aqueous phase was acidified to  $\text{pH} = 3$  with an aqueous solution of  $\text{HCl}$  (1N) and washed with  $\text{CH}_2\text{Cl}_2$  before concentration under vacuum affording a white solid, which was washed with  $\text{MeOH}$  to give the title product, yield 49%.  $^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO):  $\delta$  2.47-2.48 (m, 2H), 2.82-2.87 (m, 4H), 2.96-3.015 (m, 2H), 3.6-3.3-63 (m, 2H +  $\text{H}_2\text{O}$ ), 7.49 (s, 1H), 8.53 (s, 1H),  $^{13}\text{C}$  NMR (300 MHz,  $\text{D}_2\text{O}$ ):  $\delta$  30.3, 52.0, 56.1, 63.9, 121.4, 125.6, 147.9, 149.0, 154.9, 172.6. Mass spectrum,  $M + 1 = 271$ .

#### 10 Step 4

1-(1,3-Benzodioxol-5-yl)-8-([5-chloro-2-(2-morpholin-4-ylethyl)isonicotinoyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

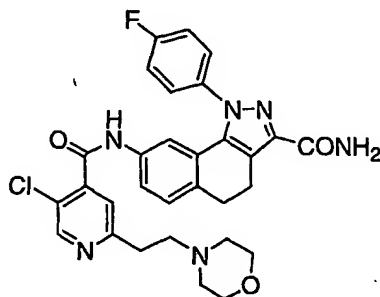


15 **[00298]** The product of step 4 was synthesized by the same procedure as in Example 211, starting with 8-amino-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (0.3 g, 0.86 mmol), 2-(Morpholin-4-ylethyl)-5-chloroisonicotinic acid hydrochloride (step 2) (0.399 g, 0.86 mmol), HATU (0.48 g, 1.28 mmol) and  $\text{Et}_3\text{N}$  (0.511 g, 0.70 mL, 5.05 mmol) in 6 mL of DMF. Purification  
20 by chromatography on silica gel ( $\text{CH}_2\text{Cl}_2$  /  $\text{MeOH}$ : 11/1) afforded the title compound as a yellow solid, yield 41%.  $^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO):  $\delta$  2.38 (s (broad), 4H), 2.62 (t, 2H,  $J = 7.12$  Hz), 2.87-2.92 (m, 4H + 2H), 3.52 (t, 4H,  $J = 3.23$ ), 6.07 (s, 2H), 6.94 (dd, 1H,  $J = 8.2$  Hz, 1.88 Hz), 6.99-7.01 (m, 1H), 7.09 (d, 1H,  $J = 1.88$  Hz), 7.24 (s, 1H), 7.27-7.31 (m, 2H), 7.38 (dd, 1H,  $J = 8.2$  Hz, 1.88  
25 Hz), 7.43 (s, 1H), 7.49 (s, 1H), 8.58 (s, 1H), 10.44 (s, 1H). Mass spectrum,  $M + 1 = 262$ .

## Example 461

8-{[5-Chloro-2-(2-morpholin-4-ylethyl)isonicotinoyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

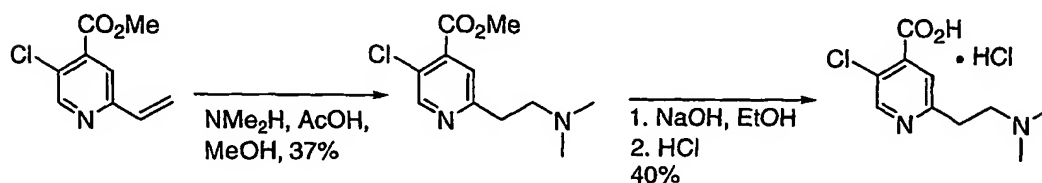
5



[00299] The title compound was synthesized by the same procedure as in Example 211, starting with 8-amino-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (0.489 g, 1.52 mmol), 2-(Morpholin-4-ylethyl)-5-chloroisonicotinic acid hydrochloride (step 3 of Example 460) (0.7 g, 2.27 mmol), HATU (0.852 g, 2.24 mmol) and Et<sub>3</sub>N (0.885 g, 1.22 mL, 8.75 mmol) in 10 mL of DMF. Purification by preparative reverse phase HPLC afforded the title compound as a white solid, yield 25 %. <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): δ 2.35 (s (broad), 4H), 2.58 (t, 2H, J = 7.58 Hz), 2.84-2.90 (m, 4H + 2H), 3.54 (t, 4H, J = 4.36 Hz), 7.18 (s, 1H), 7.25 (s, 1H), 7.28-7.37 (m, 4H), 7.39 (s, 1H), 7.53-7.56 (m, 3H), 8.55 (s, 1H), 10.41 (s, 1H). Mass spectrum, M + 1 = 576.

Example 462 was prepared using a synthesis method similar to that of Example 460 and 461, differing only in the amine added to the methyl 2-vinyl-5-chloropyridine.

## SCHEME XXXII



25

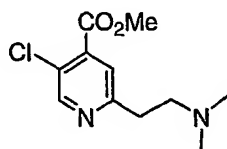
## Example 462

8-((5-Chloro-2-[2-(dimethylamino)ethyl]isonicotinoyl)amino)-1-(4-fluorophenyl)-  
4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

5

## Step 1

Methyl 5-chloro-2-[2-(dimethylamino)ethyl]isonicotinate



10

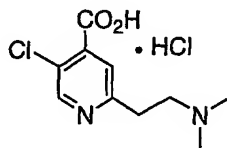
[00300] A mixture of methyl 2-vinyl-5-chloroisonicotinate (step 2 of  
Example 460) (2.48 g, 12.5 mmol), methylamine (2 M solution in MeOH) (11.5  
mL, 23 mmol) and acetic acid (1.38 g, 1.32 mL, 23 mmol) in 3 mL MeOH was  
heated at 78°C in a sealed tube for 3 days. The reaction mixture was concentrated  
under vacuum and the resulting residue basified to pH = 8 to 9 with a saturated  
aqueous solution of Na<sub>2</sub>CO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were  
dried over MgSO<sub>4</sub>. Purification by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>) afforded  
the title compound in 37% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.29 (s, 6H), 2.71  
(t, 2H, *J* = 7.36 Hz), 2.97 (t, 2H, *J* = 7.36 Hz), 3.9 (s, 3H), 7.5 (s, 1H), 8.56 (s, 1H),  
<sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): δ 35.5, 45.4, 53.1, 59.0, 123.8, 127.8, 137.1, 150.8,  
159.3, 164.9. Mass spectrum, *M* + 1 = 243.

20

## Step 2

5-Chloro-2-[2-(dimethylamino)ethyl]isonicotinic acid hydrochloride

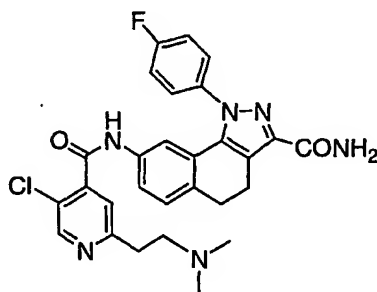
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[00301] An aqueous solution of NaOH (1 mol/L) (5.8 mL, 5.8 mmol) was added to a solution of methyl 5-chloro-2-[2-(dimethylamino)ethyl]isonicotinate (step 1) (1.41 g, 5.8 mmol) in 15 mL MeOH. The reaction mixture was stirred at room temperature for 3 h and concentrated under vacuum. The basic aqueous residue was washed once with CH<sub>2</sub>Cl<sub>2</sub>. The aqueous phase was acidified to pH = 3 with an aqueous solution of HCl (1N) and washed with CH<sub>2</sub>Cl<sub>2</sub> before concentration under vacuum affording a white solid, which was washed with MeOH to give the title product, yield 40 %. <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O): δ 2.76 (s, 6H), 3.12 (t, 2H, *J* = 7.24 Hz), 3.38 (t, 2H, *J* = 7.24 Hz), 7.30 (s, 1H), 8.40 (s, 1H). Mass spectrum, *M* + 1 = 229.

### Step 3

8-({5-Chloro-2-[2-(dimethylamino)ethyl]isonicotinoyl} amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



[00302] The title compound was synthesized by the same procedure as in Example 211, starting with 8-amino-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (0.3 g, 0.86 mmol) (0.478 g, 1.48 mmol), 2-(Morpholin-4-ylethyl)-5-chloroisonicotinic acid hydrochloride (step 3 of Example 460) (0.59 g, 2.22 mmol), HATU (0.833 g, 2.19 mmol) and Et<sub>3</sub>N (0.871 g, 1.2 mL, 8.6 mmol) in DMF (8 mL). Purification by preparative reverse phase HPLC afforded the title compound as a white solid in 33% yield. <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO): δ 2.10 (s, 6H), 2.54 (t, 2H, *J* = 7 Hz), 2.81-2.90 (m, 6H), 7.18 (s, 1H), 7.26-7.37 (m, 6H), 7.52-7.56 (m, 3H), 8.54 (s, 1H), 10.42 (s, 1H). Mass spectrum, *M* + 1 = 534

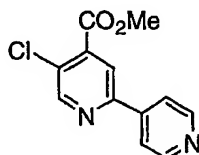
## Example 463

8-[[[(5-Chloro-2,4'-bipyridin-4-yl)carbonyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

5

## Step 1

Methyl 5-chloro-2,4'-bipyridine-4-carboxylate



10

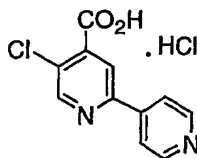
[00303] The product of step 1 was synthesized by the same procedure as for methyl 2-vinyl-5-chloroisonicotinate (step 2 of Example 461) starting with methyl 2,5-dichloroisonicotinate (step 1 of Example 460) (1.4 g, 6.8 mmol), 4-tributylstanylpiperidine (2.5 g, 6.8 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (45 mg) in 20 mL of dioxane. The reaction mixture was refluxed for 7 days. Purification by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 18/1) afforded the title compound as a colorless oil, yield 44 %. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 4.02 (s, 3H), 7.89-7.91 (m, 2H), 8.17 (s, 1H), 8.76 (d, broad, 2H, J = 6.0 Hz), 8.81 (s, 1H). Mass spectrum, M + 1 = 249.

15

20

## Step 2

5-Chloro-2,4'-bipyridine-4-carboxylic acid hydrochloride



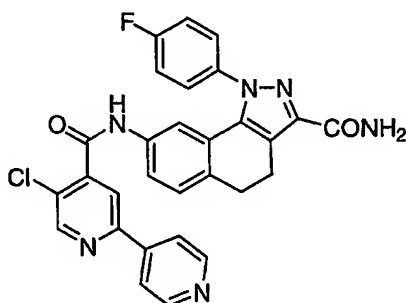
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[00304] The compound of step 2 was synthesized by the same procedure as for 5-chloro-2-[2-(dimethylamino)ethyl]isonicotinic acid hydrochloride (step 2 of

Example 462) starting with the product of step 1 (0.755 g, 3 mmol) and NaOH (1 mol/L) (4.5 mL, 4.5 mmol) in 5 mL MeOH. The reaction mixture was stirred at room temperature for 1h before acidification to pH = 2 with an aqueous HCl (1N) solution. The acidic mixture was washed once with CH<sub>2</sub>Cl<sub>2</sub>. White needles  
 5 crystallized from the acidic aqueous layer. These needles were filtered and washed with water to give the title compound in 36% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.1 (dd, 2H, J = 4.6 Hz, 1.6 Hz), 8.4 (s, 1H), 8.72 (dd, 2H, J = 4.6 Hz, 1.6 Hz), 8.9 (s, 1H). Mass spectrum, M + 1 (-HCl) = 235.

### 10 Step 3

8-[[[(5-Chloro-2,4'-bipyridin-4-yl)carbonyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



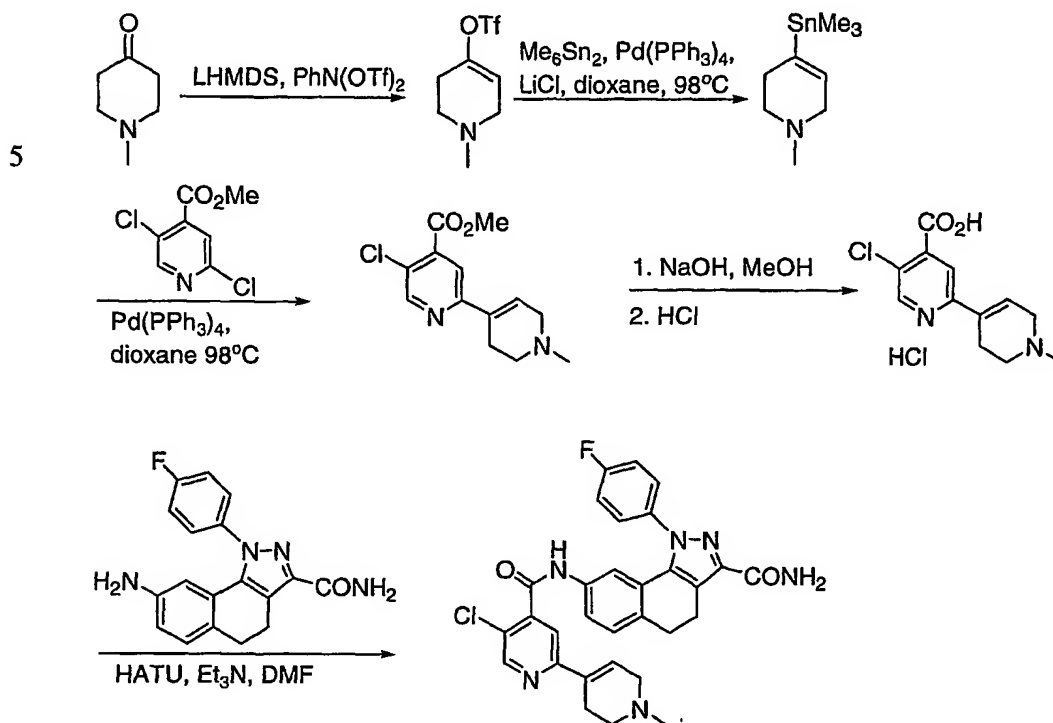
15

[00305] The title compound was synthesized by the same procedure as in Example 211 starting with 8-amino-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (0.3 g, 0.86 mmol) (0.227 g, 0.7 mmol), the product of step 2 (0.287 g, 1.0 mmol), HATU (0.395 g, 1 mmol) and Et<sub>3</sub>N (0.413 g, 1.2 mL, 4 mmol) in DMF (6 mL). Crystallization from CH<sub>3</sub>CN afforded the title  
 20 compound as a white solid, yield 45%. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 2.9-2.95 (m, 4H), 7.26 (d, 1H, J = 2 Hz), 7.28 (s, 1H), 7.34-7.42 (m, 4H), 7.55 (s, 1H), 7.57-7.6 (m, 2H), 8.07 (dd, 2H, J = 4.6 Hz, 1.5 Hz), 8.3 (s, 1H), 8.7 (dd, 2H, J = 4.6 Hz, 1.5 Hz), 8.86 (s, 1H), 10.5 (s, 1H). Mass spectrum, M + 1 = 539.

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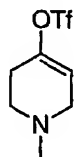
[00306] Example 464 was synthesized by the following synthesis method. The first two bicyclic compounds were not isolated pure, but subjected to

successive reactions as described in step 3 to give 8-[[[(5-chloro-1'-methyl-1',2',3',6'-tetrahydro-2,4'-bipyridin-4-yl)carbonyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide.



# 10 Step 1

1-Methyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate



- 15 [00307] LiHMDS (1M, THF) (48.6 mL, 48.6 mmol) was added to a solution of 1-methyl-4-piperidone (5 g, 5.43 mL, 44.2 mmol) in 80 mL THF at  $-75^{\circ}\text{C}$ . The mixture was stirred at this temperature for 2 h and warmed up to  $-50^{\circ}\text{C}$ . A solution of N-phenyltrifluoro-methanesulfonimide (17.36 g, 48.6 mmol) in 55 mL THF was added to the reaction mixture, which was then allowed to warm up to room



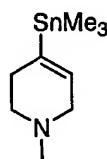
temperature over a period of 3 h. The volatiles were removed under vacuum.

Purification of the resulting residue by chromatography on silica gel

(EtOAc/hexanes: 7/3) afforded the title compound in 73% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.36 (s, 3H), 2.43-2.45 (m, 2H), 2.65 (t, 2H, *J* = 5.8 Hz), 3.05-3.07 (m, 2H), 5.68 - 5.70 (m, 1H).

## Step 2

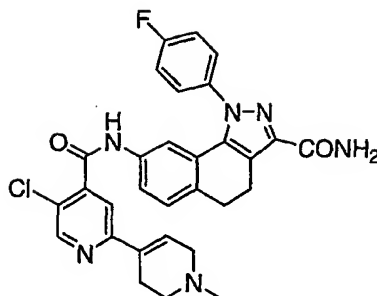
1-Methyl-4-(trimethylstannyl)-1,2,3,6-tetrahydropyridine



[00308] Pd(PPh<sub>3</sub>)<sub>4</sub> (0.31 g, 0.26 mmol) was added to a degassed mixture of 1-methyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (step 1) (3.28 g, 13.3 mmol), hexamethylditin ( 4.60 g, 14 mmol), LiCl (1.73 g, 40 mmol) and a few crystals of 2,6-di-tert-butyl-4-methylphenol in 60 mL dioxane. The reaction mixture was heated at 98°C for 4 h. After cooling the reaction mixture was poured into an aqueous solution of KF and extracted with Et<sub>2</sub>O. The organic extracts were washed once with H<sub>2</sub>O and once with brine before being dried over MgSO<sub>4</sub>. The residue obtained after removal was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH : 10/1) to afford the title compound in a 41% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.0 (t, 9H, *J*<sub>Sn-H</sub> = 26.4 Hz), 2.21 (s, 3H), 2.23-2.27 (m, 2H), 2.39 (t, 2H, *J* = 5.6 Hz), 2.82-2.85 (m, 2H), 5.70 - 5.72 (m, 1H).

## Step 3

8-{[(5-chloro-1'-methyl-1',2',3',6'-tetrahydro-2,4'-bipyridin-4-yl)carbonyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



[00309] Pd(PPh<sub>3</sub>)<sub>4</sub> (30 mg, 0.025 mmol) was added to a degassed mixture of the product of step 2 (1.82 g, 7 mmol) and methyl 2,5-dichloroisonicotinate (step 1 of

5 Example 460) (0.96 g, 4.66 mmol) in 10 mL of dioxane. The reaction mixture was kept at 98°C overnight. After cooling the reaction mixture was poured into an aqueous solution of KF and extracted with EtOAc. The organic extracts were washed once with H<sub>2</sub>O and once with brine before being dried over MgSO<sub>4</sub>. The residue, obtained after removal of the solvents, was purified by chromatography on

10 silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 15/1) to afford 0.606 g of a 2/1 mixture of the methyl 5-chloro-1'-methyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-4-carboxylate and the product of step 2 which was dissolved in 5 mL of MeOH and reacted at room temperature with an aqueous solution of NaOH (1M) (2.5 mL, 2.5 mmol) for 1.5 h. The reaction mixture was acidified to pH = 2 with an aqueous solution of HCl (1N)

15 and concentrated to give a white solid residue. This residue was reacted with 8-amino-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (0.52 g, 1.6 mmol) in 10 mL DMF in the presence of Et<sub>3</sub>N (0.94 g, 1.3 mL, 9.3 mmol) and HATU (0.906 g, 2.38 mmol). After stirring 1.5 h, the mixture was concentrated and a white solid precipitated upon addition of water. The solid was filtered,

20 dissolved in THF and dried over MgSO<sub>4</sub>. Preparative HPLC afforded the title compound in 36% yield. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 2.25 (s, 3H), 2.51-2.53 (m, 4H), 2.86-2.91 (m, 4H), 3.04 (s, broad, 2H), 6.73 (s, broad, 1H), 7.19 (t, 1H, J = 2.5 Hz), 7.25 (s, 1H), 7.29-7.38 (m, 4H), 7.52-7.56 (m, 3H), 7.59 (s, 1H), 8.59 (s, 1H), 10.4 (s, 1H). Mass spectrum, M + 1 = 558

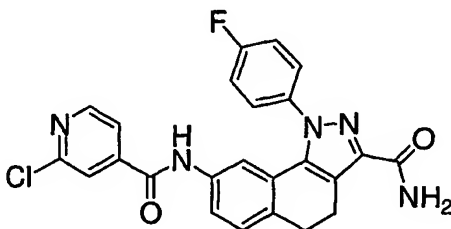
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## Example 465

1-(4-Fluorophenyl)-8-[(2-morpholin-4-ylisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

## 5 Step 1

8-[(2-Chloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



10

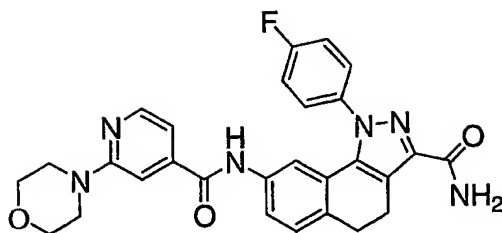
[00310] The product of Example 244 (8-amino-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (8.46 mmol), 2-chloroisonicotinic acid (12.70 mmol), HATU (12.63 mmol), and 4.2 mL triethylamine were dissolved in 42 mL of DMF. The mixture was stirred at r.t. for 4 h. The solvent was then partially stripped and the residue suspended in water, filtered, and washed with water. The solid was triturated in water, dissolved in acetonitrile, decolorized with activated carbon, dried over MgSO<sub>4</sub>, and recrystallized from acetonitrile. Mp: 258-262°C. Mass spectrum: M + 1 = 462. <sup>1</sup>H NMR (δ, d<sub>6</sub>-DMSO, 400 MHz): 2.83-2.95 (m, 4H); 7.26 (s, 1H); 7.30-7.42 (m, 5H); 7.50-7.58 (m, 3H); 7.65-7.68 (m, 1H); 7.78 (s, 1H); 8.53 (d, 1H, J = 5.1 Hz); 10.36 (s, 1H).

20

## Step 2

1-(4-Fluorophenyl)-8-[(2-morpholin-4-ylisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

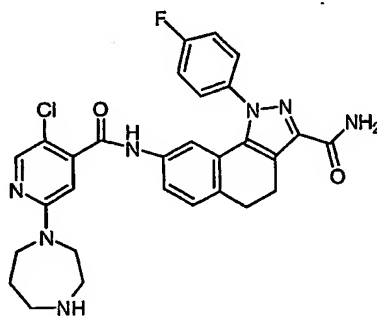
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[00311] The product of step 1 (2.17 mmol) and morpholine (32.7 mmol) were dissolved in 10 mL N,N-dimethylacetamide. The reaction mixture was placed under nitrogen and stirred in an oil bath at 80°C for 160 h then 100°C for 172 h. The mixture was partially stripped of solvent then added to water causing a precipitate, filtered, and washed with water. The solid was recrystallized from acetonitrile, and triturated in diethyl ether, ethyl acetate, acetonitrile, and ethanol. The product was dissolved in tetrahydrofuran, dried over MgSO<sub>4</sub>, and the solvent stripped. Finally, the product was dissolved in ethanol followed by stripping to remove trapped solvents. Mp: 269-274°C (decomp.). Mass spectrum: M + 1 = 513. <sup>1</sup>H NMR (δ, d<sub>6</sub>-DMSO, 400 MHz): 2.56-2.59 (m, 4H); 3.44 (t, 4H, J = 4.8 Hz); 3.66 (t, 4H, J = 4.8 Hz); 6.88-6.92 (m, 1H); 7.02 (s, 1H); 7.24-7.43 (m, 6H); 7.50-7.58 (m, 3H); 8.19 (d, 1H, J = 5.1 Hz); 10.12 (s, 1H).

#### Example 466

8-([5-chloro-2-(1,4-diazepan-1-yl)isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

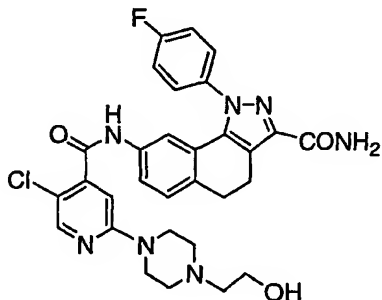


[00312] The title compound was synthesized by the same procedure as in Example 214 starting with 8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-

4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (Example 248) (1 g, 2 mmol) and homopiperazine (4 g, 40 mmol) in 5 mL EtOH. The reaction was run at 100°C for 24 h. The white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH to afford the title product, yield: 82%. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 1.68-1.72 (m, 2H), 2.63 (t, 2H, *J* = 5.84 Hz), 2.79 (t, 2H, *J* = 5 Hz), 2.91-2.93 (m, 4H), 3.59 (t, 2H, *J* = 5 Hz), 3.64 (t, 2H, *J* = 5.84 Hz), 6.62 (s, 1H), 7.2 (d, 1H, *J* = 2 Hz), 7.28-7.4 (m, 4H), 7.44 (dd, 1H, *J* = 8.2 Hz, 2 Hz), 7.55-7.60 (m, 3H), 8.08 (s, 1H), 10.32 (s, 1H). Mass spectrum, *M* + 1 = 561.

#### 10 Example 467

8-({5-Chloro-2-[4-(2-hydroxyethyl)piperazin-1-yl]isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

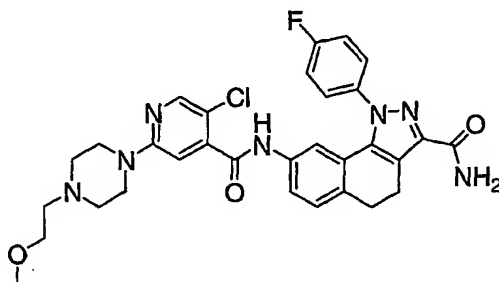


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[00313] The title compound was synthesized by the same procedure as in Example 214 starting with 8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (Example 248) (0.8 g, 1.6 mmol) and 1-(2-hydroxyethyl)piperazine (4.19 g, 3.94 mL, 32 mmol). The reaction was run at 100°C for 24 h. The white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH and finally triturated with CHCl<sub>3</sub> to afford the title product, yield: 66%. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 2.38 (t, 2H, *J* = 6.2 Hz), 2.44 (t, 4H, *J* = 4.7 Hz), 2.87-2.93 (m, 4H), 3.45-3.52 (m, 4H + 2H), 4.39 (t, 1H, *J* = 5.3 Hz), 6.87 (s, 1H), 7.2 (d, 1H, *J* = 2 Hz), 7.27 (s, 1H), 7.29-7.38 (m, 3H), 7.4 (dd, 1H, *J* = 8.2 Hz, 2 Hz), 7.54-7.58 (m, 3H), 8.12 (s, 1H), 10.31 (s, 1H). Mass spectrum, *M* + 1 = 591.

## Example 468

8-({5-Chloro-2-[4-(2-methoxyethyl)piperazin-1-yl]isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



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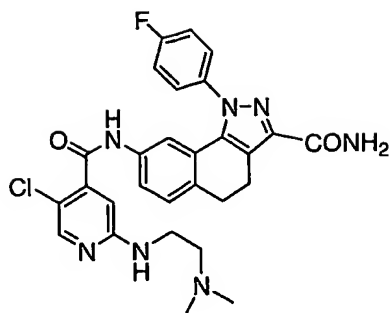
**[00314]** The title compound of Example 248 (8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (1.61 mmol) and 1-(2-methoxyethyl)-piperazine (16.25 mmol) were combined with 4.0 mL of DMA. . The reaction mixture was placed under nitrogen and stirred in an oil bath at 100°C for 25 h. The mixture was added to water causing a precipitate, filtered, and washed with water. The product was dissolved in tetrahydrofuran, dried over MgSO<sub>4</sub>, and the solvent stripped. The product was purified by nearly dissolving in ethanol, adding acetonitrile, the solid triturated in the solvent mix, the solvent partially stripped, and slurry filtered. Elemental analysis: 61.65% C, 5.22% H, 16.04% N (theory: 61.64% C, 5.17% H, 16.23% N). Mp: 238-240°C. Mass spectrum: M + 1 = 604.

15

## Example 469

8-[(5-Chloro-2-{[2-(dimethylamino)ethyl]amino}isonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

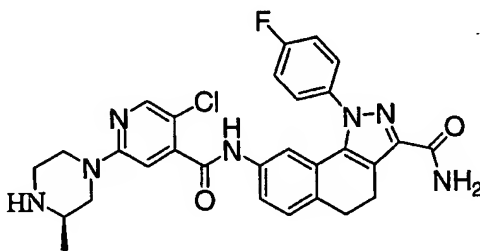
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**[00315]** The title compound was synthesized by the same procedure as in Example 214 starting with 8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (Example 248) (1 g, 2 mmol) and N,N-dimethylethylenediamine (3.55 g, 4.42 mL, 40 mmol). The reaction was run at 100°C for 24 h. The white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH and finally purified by reverse phase preparative HPLC to afford the title product, yield: 14%. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 2.13 (s, 6H), 2.34 (t, 2H, *J* = 6.5 Hz), 2.87 - 2.92 (m, 4H), 3.29 - 3.30 (m, 2H), 6.49 (s, 1H), 6.78 (t, 1H, *J* = 5.3 Hz), 7.2 (d, 1H, *J* = 2 Hz), 7.27 (s, 1H), 7.29 - 7.40 (m, 4H), 7.53 - 7.58 (m, 3H), 7.99 (s, 1H), 10.3 (s, 1H). Mass spectrum, *M* + 1 = 549.

#### Example 470

**8-((5-Chloro-2-[(3R)-3-methylpiperazin-1-yl]isonicotinoyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide**



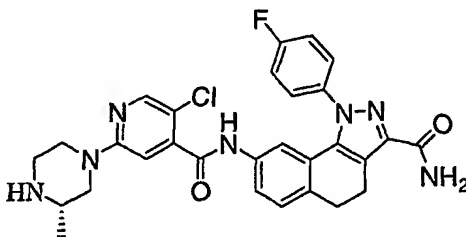
**[00316]** The title compound of Example 248 (8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (2.62 mmol) and (R)-2-methylpiperazine (25.6 mmol) were

combined with 6.5 mL of DMA. The reaction mixture was placed under nitrogen and stirred in an oil bath at 100°C for 15.5 h. The mixture was then added to water, causing a precipitate, which was filtered and washed with water. The solid was dissolved in acetonitrile, dried over MgSO<sub>4</sub>, and the solvent stripped. Mp., 275-  
5 278°C (decomp.). Mass spectrum: M + 1 = 560.

#### Example 471

8-({5-Chloro-2-[(3S)-3-methylpiperazin-1-yl]isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

10



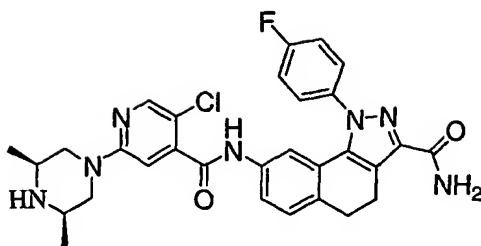
[00317] The title compound of Example 248 (8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (2.63 mmol) and (S)-2-methylpiperazine (25.1 mmol) were  
15 combined with 6.5 mL N,N-dimethylacetamide. The reaction mixture was placed under nitrogen and stirred in an oil bath at 100°C for 15.5 h. The mixture was then added to water causing a precipitate, which was filtered, and washed with water. The solid was dissolved in acetonitrile, dried over MgSO<sub>4</sub>, and the solvent stripped.  
20 Mp: 275-278°C (decomp.). Mass spectrum: M + 1 = 560.

#### Example 472

8-({5-Chloro-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

25

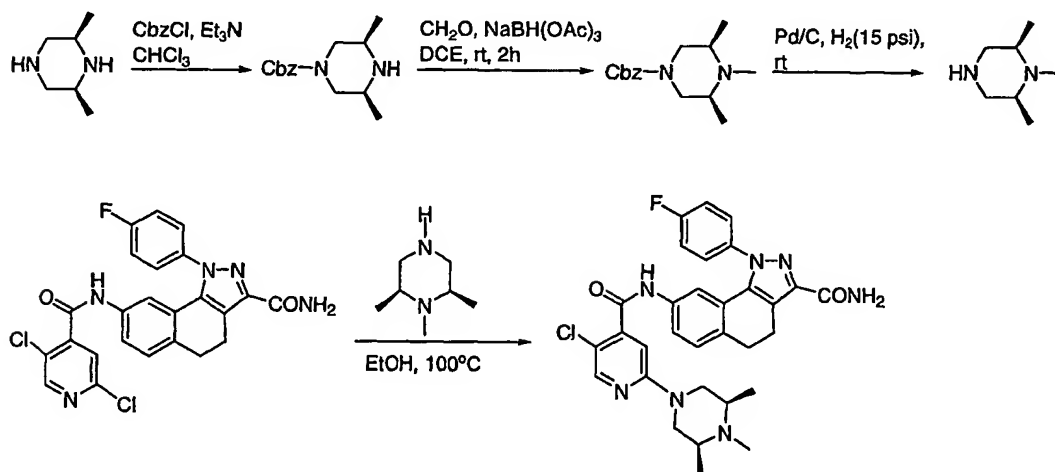




[00318] The title compound of Example 248 (8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (2.62 mmol) and cis-2,6-dimethyl piperazine (26.2 mmol), were combined with 6.5 mL DMA. The reaction mixture was placed under nitrogen and stirred in an oil bath at 100°C for 24 h. The mixture was then added to water, causing a precipitate, which was filtered and washed with water. The solid was dissolved in acetonitrile, dried over MgSO<sub>4</sub>, and the solvent stripped. Mp: 250°C (decomp.). Mass spectrum: M + 1 = 574.

[00319] Examples 473, 474, 475 were synthesized by the following synthesis method, illustrated for 473.

15 SCHEME XXXIII

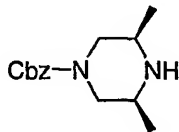


20 Example 473

8-({5-Chloro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

## Step 1

Benzyl (3R,5S)-3,5-dimethylpiperazine-1-carboxylate



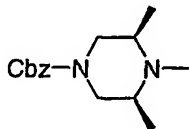
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[00320] Benzyl chloroformate (9.7g, 8.12 mL, 54.1 mmol) was slowly added to a mixture of 2,6-dimethylpiperazine (6.25g, 54.7 mmol) and Et<sub>3</sub>N (5.53g, 7.6 mL, 54.7 mmol) in 100 mL CHCl<sub>3</sub>. The reaction mixture was stirred at room temperature for 4h. Water was added and the organic phase separated and dried over MgSO<sub>4</sub>. Purification by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 12/1) afforded the title compound in 60% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.04 (d, 6H, J = 6.2 Hz), 1.46 (s, broad, 1H), 2.38 (m, broad, 2H), 2.78 (s, broad, 2H), 3.99 - 4.03 (m, broad, 2H), 5.12 (s, 2H), 7.34 - 7.36 (m, 5H), <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): δ 19.5, 50.9, 67.3, 128.1, 128.2, 128.7, 137.0, 155.3.

15

## Step 2

Benzyl (3R,5S)-3,4,5-trimethylpiperazine-1-carboxylate



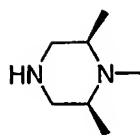
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[00321] NaBH(OAc)<sub>3</sub> (2.96 g, 14 mmol) was added to a mixture of the product of step 1 (2.34 g, 10 mmol) and formaldehyde (0.86 g, 0.79 mL, 10 mmol) in 35 mL dichloroethane. The reaction mixture was stirred at room temperature for 1 h 40 min and quenched by adding an aqueous saturated solution of NaHCO<sub>3</sub>. The product was extracted with EtOAc and dried over MgSO<sub>4</sub>. Evaporation of the volatiles afforded the titled compound in 76% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.09 (d, 6H, J = 6.1 Hz), 2.16-2.17 (m, 2H), 2.25 (s, 3H), 2.65 (m, broad, 2H), 3.95 (m, broad, 2H), 5.13 (s, 2H), 7.33 - 7.36 (m, 5H). Mass spectrum, M + 1 = 263.

25

## Step 3

(2R,6S)-1,2,6-Trimethylpiperazine



5

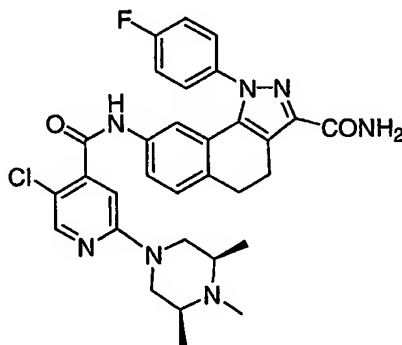
[00322] A mixture of the product of step 2 (2.75 g, 10 mmol) and Pd/C (5%, 1.1 g) in 20 mL MeOH was reacted for 2 h at room temperature under H<sub>2</sub> (15psi). The mixture was filtered through Celite and the filtrate evaporated to afford the title compound in 80% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.0 (d, 6H, J = 6.1 Hz), 1.78 (m, broad, 1H), 2.0-2.05 (m, 2H), 2.21 (s, 3H), 2.5 (t, 2H, J = 10.7), 2.82 (dd, 2H, J = 12.5 Hz, 1.8 Hz). Mass spectrum, M + 1 = 129.

10

## Step 4

8-({5-Chloro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

15



[00323] The title compound was synthesized by the same procedure as in Example 214 starting with 8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (0.49 g, 1.0 mmol) and (2R,6S)-1,2,6-trimethylpiperazine (step 3) (1.03 g, 8.0 mmol) in 5 mL of EtOH. The reaction was run at 100°C for 5 days. The off-white precipitate that formed in the

20

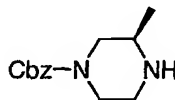
crude reaction mixture was filtered and washed with EtOH to afford the title compound in 77% yield. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 1.01 (d, 6H, *J* = 12.3 Hz), 2.05 (m, broad, 2H), 2.13 (s, 3H), 2.47-2.53 (2H, m, overlaps with DMSO), 2.88-2.93 (m, 4H), 4.11 (d, 2H, *J* = 12.3 Hz), 6.92 (s, 1 H), 7.21 (d, 1H, *J* = 2.0Hz), 7.27 (s, 1H), 7.3-7.38 (m, 3H), 7.41 (dd, 1H, *J* = 8.2 Hz, 2.0 Hz), 7.54-7.58 (m, 3H), 8.11 (s, 1H), 10.32 (s, 1H). HRMS calc. for C<sub>31</sub>H<sub>32</sub>ClFN<sub>7</sub>O<sub>2</sub> 588.2285, found 588.2212.

#### Example 474

8-({5-Chloro-2-[(3R)-3,4-dimethylpiperazin-1-yl]isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

#### Step 1

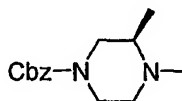
Benzyl (3R)-3-methylpiperazine-1-carboxylate



**[00324]** The product of step 1 was synthesized by the same procedure as for compound of step 1 of Example 473 starting with 2-(R)-methylpiperazine (6 g, 59.9 mmol), triethylamine (6.04 g, 8.32 mL, 59.7 mmol) and benzyl chloroformate (10.62 g, 59.2 mmol) in 100 mL of CHCl<sub>3</sub>. Purification by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 12/1) afforded the title compound in 30% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.05 (d, 3H, *J* = 6.2 Hz), 1.59 (s, 1H), 2.47 (s, broad, 1H), 2.71 - 2.9 (m, 4H), 4.02 (s, broad, 1H), 5.13 (s, 2H), 7.30 - 7.36 (m, 5H).

#### Step 2

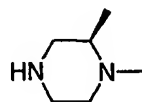
Benzyl (3R)-3,4-dimethylpiperazine-1-carboxylate



[00325] The title compound of step 2 was synthesized by the same procedure as for the compound of step 2 of Example 473 starting with compound of step 1 (3.77 g, 16 mmol), formaldehyde (1.46 g, 1.34 mL, 16 mmol), and NaHB(OAc)<sub>3</sub> (4.98 g, 23 mmol) in 60 mL of dichloroethane to afford the title compound in 95 %  
5 yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.05 (d, 3H, J = 6.24 Hz), 2.02 - 2.08 (m, 1H), 2.13-2.21 (m, 1H), 2.28 (s, 3H), 2.72-2.76 (m, 2H), 3.08 (t, 1H, J = 1.2 Hz), 3.95 - 3.99 (m, 2H), 5.12 (s, 2H), 7.32 - 7.36 (m, 5H).

Step 3

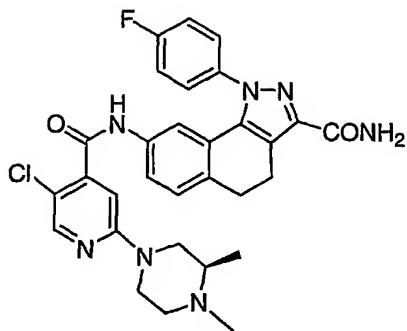
10 (2R)-1,2-Dimethylpiperazine



[00326] The title compound of step 3 was synthesized by the same procedure as for step 3 of Example 473 starting with the compound of step 2 (3.78 g, 15.2  
15 mmol), (Pd/C (5%, 1.6g) in 30 mL of MeOH under H<sub>2</sub> (15 psi). The reaction mixture was stirred 4 h to afford the title compound in 53% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.03 (d, 3H, J = 6.24 Hz), 1.96-2.03 (m, 1H), 2.12 - 2.21 (m, 1H), 2.27 (s, 1H), 2.34 (s, broad, 1H), 2.45 - 2.52 (m, 1H), 2.73 - 2.92 (m, 4H). Mass  
20 spectrum, M + 1 = 115. HRMS calc. for C<sub>6</sub>H<sub>15</sub>N<sub>2</sub> 115.1230, found 115.1199.

Step 4

8-({5-Chloro-2-[(3R)-3,4-dimethylpiperazin-1-yl]isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide  
25



[00327] The title compound was synthesized by the same procedure as in Example 214 starting with 8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (Example 248) (0.434 g, 0.87 mmol) and (2R)-1,2-dimethylpiperazine (step 3) (0.9 g, 7.8 mmol) in 5 mL of EtOH. The reaction was run at 100°C for 4 days. The off-white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH to afford the title compound in 55% yield. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 1.0 (d, 3H, *J* = 6.17 Hz), 1.96 - 2.0 (m, 1H), 2.05 - 2.06 (m, 1H), 2.15 (s, 3H), 2.48 - 2.54 (m, 1H), 2.74 (d, broad, 1H, *J* = 11.5 Hz), 2.85 - 2.93 (m, 4H), 4.01-4.09 (m, 2H), 6.89 (s, 1H), 7.21 (d, 1H, *J* = 2.0 Hz), 7.27 (s, 1H), 7.29 - 7.38 (m, 2H), 7.41 (dd, 1H, *J* = 8.2 Hz, 2.0 Hz), 7.53 - 7.58 (m, 2H), 8.11 (s, 1H), 10.33 (s, 1H). HRMS calc. for C<sub>30</sub>H<sub>30</sub>ClFN<sub>7</sub>O<sub>2</sub> 574.2128, found 574.2094.

15

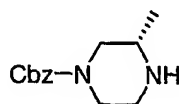
## Example 475

8-((5-Chloro-2-[(3S)-3,4-dimethylpiperazin-1-yl]isonicotinoyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

20

## Step 1

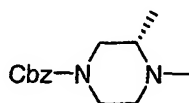
Benzyl (3S)-3-methylpiperazine-1-carboxylate



[00328] The compound of step 1 was synthesized by the same procedure as for step 1 of Example 473 starting with 2-(S)-methylpiperazine (6 g, 59.9 mmol), triethylamine (6.04 g, 8.32 mL, 59.7 mmol) and benzyl chloroformate (10.62 g, 59.2 mmol) in 100 mL CHCl<sub>3</sub>. Purification by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH: 12/1) afforded the title compound in 22% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.05 (d, 3H, *J* = 6.2 Hz), 1.89 (s, 1H), 2.48 (s, broad, 1H), 2.7-2.97 (m, 4H), 4.02 (s, broad, 1H), 5.12 (s, 2H), 7.32 - 7.35 (m, 5H).

## Step 2

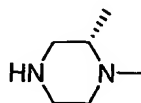
10 Benzyl (3S)-3,4-dimethylpiperazine-1-carboxylate



[00329] The compound of step 2 was synthesized by the same procedure as for step 2 for Example 473 starting with the compound of step 1 (3.1 g, 13 mmol), formaldehyde (1.2 g, 1.1 mL, 13 mmol), and NaHB(OAc)<sub>3</sub> (4.09 g, 19 mmol) in 50 mL dichloroethane to afford the title compound in 96 % yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.05 (d, 3H, *J* = 6 Hz), 2.02-2.05 (m, 1H), 2.13-2.21 (m, 1H), 2.28 (s, 3H), 2.71-2.75 (m, 2H), 3.08 (t, 1H, *J* = 1.5 Hz), 3.95 - 3.99 (m, 2H), 5.12 (s, 2H), 7.32 - 7.36 (m, 5H).

## Step 3

(2S)-2-Methylpiperazine



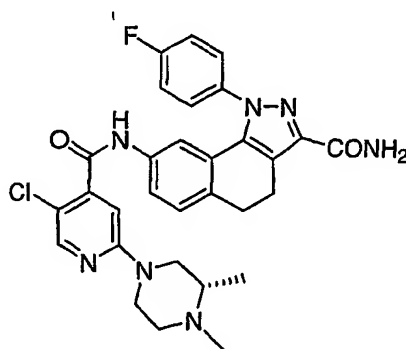
[00330] (2S)-2-Methylpiperazine was synthesized by the same procedure as for step 3 of Example 473 starting with the material from step 2 (3.1 g, 12.4 mmol), (Pd/C (5%, 1.37g) in 25 mL MeOH under H<sub>2</sub> (15 psi). The reaction mixture was

stirred 4 h to afford the title compound in 55% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.03 (d, 3H,  $J = 6.24$  Hz), 1.97 - 2.03 (m, 1H), 2.12 - 2.21 (m, 1H), 2.27 (s, 1H), 2.42 (s, broad, 1H), 2.45 - 2.52 (m, 1H), 2.73 - 2.92 (m, 4H). Mass spectrum,  $M + 1 = 115$ .

5

## Step 4

8-({5-Chloro-2-[(3S)-3,4-dimethylpiperazin-1-yl]isonicotinoyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



10

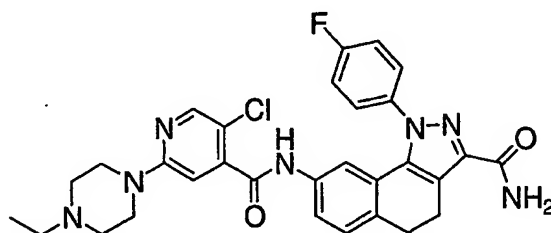
**[00331]** The title compound was synthesized by the same procedure as in Example 214 starting with 8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (Example 248) (0.380 g, 0.76 mmol) and (2S)-2-methylpiperazine (step 3) (0.79 g, 6.8 mmol) in 3 mL of EtOH. The reaction was run at 100°C for 3 days. The off-white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH to afford the title compound in 55% yield.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO):  $\delta$  1.0 (d, 3H,  $J = 6.17$  Hz), 1.96-1.98 (m, 1H), 2.02 - 2.09 (m, 1H), 2.16 (s, 3H), 2.48 - 2.54 (m, 1H), 2.74 (d, broad, 1H,  $J = 11.7$  Hz), 2.85-2.93 (m, 4H), 4.02-4.09 (m, 2H), 6.89 (s, 1H), 7.21 (d, 1H,  $J = 2.0$  Hz), 7.27 (s, 1H), 7.29 - 7.38 (m, 2H), 7.41 (dd, 1H,  $J = 8.2$  Hz, 2.0 Hz), 7.54 - 7.58 (m, 2H), 8.11 (s, 1H), 10.33 (s, 1H). HRMS calc. for  $\text{C}_{30}\text{H}_{30}\text{ClFN}_7\text{O}_2$  574.2128, found 574.2098.

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## Example 476

8-[[5-Chloro-2-(4-ethylpiperazin-1-yl)isonicotinoyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



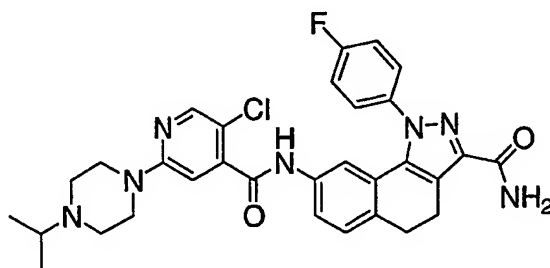
5

[00332] The title compound of Example 248 (8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (1.81 mmol) and 1-ethyl piperazine (18.1 mmol) were combined with 4.5 mL of DMA. The reaction mixture was placed under nitrogen and stirred in an oil bath at 100°C for 21 h. The mixture was added to water, causing a precipitate, which was filtered and washed with water. The solid was dissolved in acetonitrile, dried over MgSO<sub>4</sub>, filtered, and washed with acetonitrile. Mp: 251-254°C. Mass spectrum: M + 1 = 574.

15

## Example 477

8-[[5-Chloro-2-(4-isopropylpiperazin-1-yl)isonicotinoyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



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[00333] The title compound of Example 248 (8-[(2,5-dichloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (1.81 mmol) and (1-isopropyl) piperazine (18.1 mmol) were

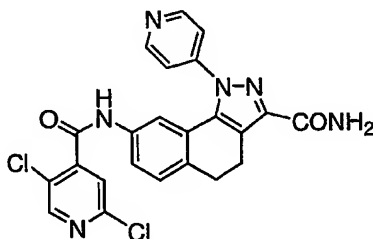
combined with 4.5 mL of DMA. The reaction mixture was placed under nitrogen and stirred in an oil bath at 100°C for 21 h. The mixture was added to water, causing a precipitate, which was filtered and washed with water. The solid was dissolved in acetonitrile, dried over MgSO<sub>4</sub>, and the solvent stripped. The product was then filtered and washed with acetonitrile. Mp: 220-226°C. Mass spectrum: M + 1 = 588.

#### Example 478

8-[[5-Chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino]-1-pyridin-4-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

#### Step 1

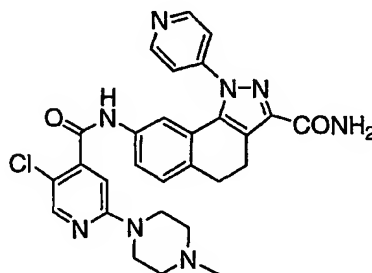
8-[(2,5-Dichloroisonicotinoyl)amino]-1-pyridin-4-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



[00334] The compound of step 1 was synthesized by the same procedure as in Example 211, starting with 8-amino-1-pyridin-4-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (1.56 g, 5.1 mmol), 2,5-dichloroisonicotinic acid (1.47 g, 7.6 mmol), HATU (2.91 g, 7.3 mmol) and Et<sub>3</sub>N (2.85 g, 2.07 mL, 28 mmol) in DMF (25 mL). The crude reaction mixture was concentrated and the product precipitated upon addition of water and filtered. Trituration in 250 mL hot CH<sub>3</sub>CN afforded the title compound as a yellow solid, yield 40%. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 2.92 (s, 4H), 7.33-7.4 (m, 3H), 7.52 (dd, 1H, *J* = 8.15 Hz, 2 Hz), 7.62-7.64 (m, 3H), 7.8 (s, 1H), 8.61 (s, 1H), 8.74 (dd, 2H, *J* = 4.6 Hz, 1.5 Hz), 10.61 (s, 1H). Mass spectrum, M + 1 = 480.

## Step 2

8-([5-Chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino)-1-pyridin-4-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



5

**[00335]** The title compound was synthesized by the same procedure as in Example 214 starting with the compound of step 1 (0.8 g, 1.66 mmol) and N-methylpiperazine (3 g, 3.34 mL, 30mmol) in 1.5 mL EtOH. The reaction was run at 100°C for 2 days. The white precipitate that formed in the crude reaction mixture was filtered and washed with EtOH to afford the title product, yield: 73%. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 2.16 (s, 3H), 2.32 (t, 4H, *J* = 4.8 Hz), 2.9 (s, 4H), 3.47 (t, 4H, *J* = 4.8 Hz), 6.89 (s, 1H), 7.34-7.38 (m, 3H), 7.54 (dd, 1H, *J* = 8.3 Hz, 2 Hz), 7.60-7.61 (m, 3H), 8.12 (s, 1H), 8.72 (dd, 2H, *J* = 4.5 Hz, 1.6 Hz), 10.4 (s, 1H). Mass spectrum, *M* + 1 = 544.

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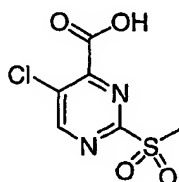
## Example 479

1-(1,3-Benzodioxol-5-yl)-8-([5-chloro-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

20

## Step 1

5-Chloro-2-(methylsulfonyl)-4-pyrimidinecarboxylic acid

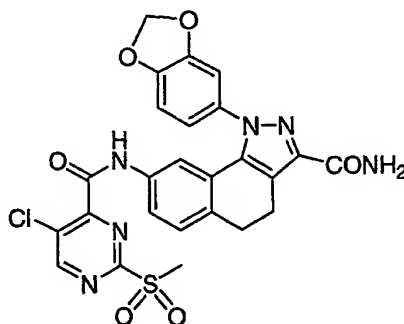


25

[00336] 5-Chloro-2-(methylsulfonyl)-4-pyrimidinecarboxylic acid was prepared by the method of Liang Yong-min, Luo Sheng-jun, Zhang Zhao-xin and Ma Yong-xiang, *Synthetic Commun.*, 32 (1), 153-157, 2002.

5 Step 2

1-(1,3-Benzodioxol-5-yl)-8-([5-chloro-2-(methylsulfonyl)pyrimidin-4-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



10

[00337] The title compound of step 2 was synthesized by the same procedure as in Example 211 starting with 5-chloro-2-(methylsulfonyl)-4-pyrimidinecarboxylic acid (step 1) (0.987 g, 4.17 mmol), Example 161, step 3 (8-amino-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide) (0.968 g, 2.78 mmol), HATU (1.58 g, 4.15 mmol) and Et<sub>3</sub>N (1.54 g, 1.12 mL, 15 mmol) in DMF (8 mL). Trituration with CH<sub>2</sub>Cl<sub>2</sub> afforded the title compound in 38% yield. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 2.86-2.91 (m, 4H), 3.42 (s, 1H), 6.05 (s, 2H), 6.94 (dd, 1H, *J* = 8.2 Hz, 2 Hz), 7 (d, 1H, *J* = 2.2 Hz), 7.1 (d, 1H, *J* = 2 Hz), 7.23-7.26 (m, 2H), 7.31-7.37 (m, 2H), 7.48 (s, 1H), 9.35 (s, 1H), 10.73 (s, 1H).

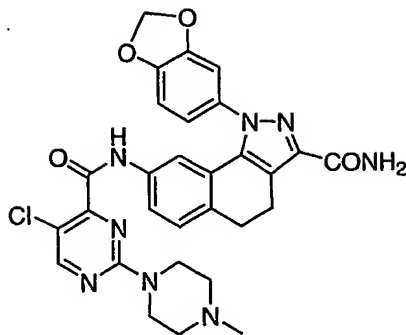
15

20 Mass spectrum, *M* + 1 = 567.

Step 3

1-(1,3-Benzodioxol-5-yl)-8-([5-chloro-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

25



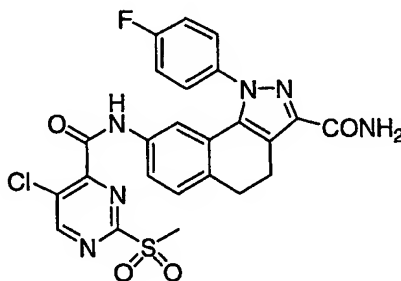
[00338] The title compound was synthesized by the same procedure as in Example 214 starting with the compound of step 2 (0.625 g, 1.1 mmol) and N-methylpiperazine (1.98 g, 2.2 mL, 20 mmol) in 3 mL EtOH. The reaction was run at 95°C for 2.5 h. The volatiles were removed and the residue partitioned between H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub>. The organics were dried over MgSO<sub>4</sub>. Purification by reverse phase preparative HPLC afforded the title product in 16% yield. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 2.18 (s, 3H), 2.33 (t, 4H, J = 4.7 Hz), 2.86-2.92 (m, 4H), 3.67 (t, 4H, J = 4.7 Hz), 6.08 (s, 2H), 6.94 (dd, 1H, J = 8.2 Hz, 2.1 Hz), 7 (d, 1H, J = 8.2 Hz), 7.1 (d, 1H, J = 2 Hz), 7.27-7.31 (m, 2H), 7.4 (dd, 1H, J = 8.2 Hz, 2 Hz), 7.49 (s, 1H), 8.5 (s, 1H), 10.34 (s, 1H). Mass spectrum, M + 1 = 567.

#### Example 480

8-([5-Chloro-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]carbonyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

#### Step 1

8-([5-Chloro-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]carbonyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

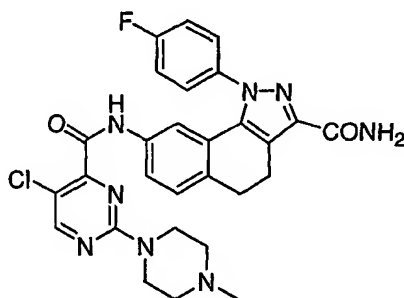


[00339] The compound of step 1 was synthesized by the same procedure as in Example 211 starting with the compound of step 1 of Example 479 (2.7 g, 11.4 mmol), 8-amino-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide (2.45 g, 7.6 mmol), HATU (4.32 g, 11.3 mmol) and Et<sub>3</sub>N (2.17 g, 3 mL, 21 mmol) in DMF (8 mL). Purification by preparative reverse phase HPLC afforded the title compound in 62% yield. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 2.88-2.92 (m, 4H), 3.41 (s, 3H), 7.22 (s, broad, 1H), 7.25 (s, broad, 1H), 7.34-7.37 (m, 4H), 7.52-7.58 (m, 3H), 9.34 (s, 1H), 10.72 (s, 1H). Mass spectrum, M + 1 = 541.

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## Step 2

8-([5-Chloro-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]carbonyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



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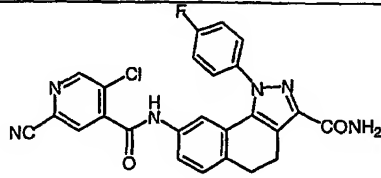
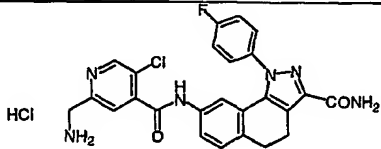
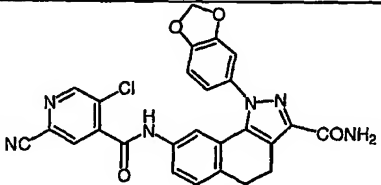
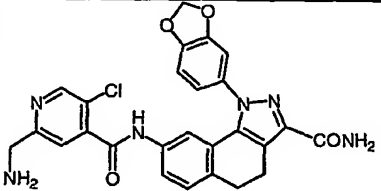
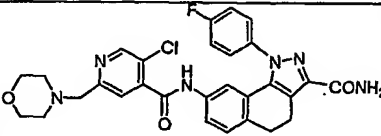
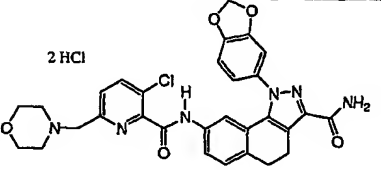
[00340] The title compound was synthesized by the same procedure as in Example 214 starting with the material from step 1 (0.9 g, 1.66 mmol) and N-methylpiperazine (1.66 g, 1.84 mL, 16.5 mmol) in 3 mL EtOH. The reaction was run at 45°C for 7 h. The yellow precipitate that formed in the crude reaction mixture was filtered and purified by reverse phase preparative HPLC to afford the title product in 15% yield. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 2.18 (s, 3H), 2.32 (t, 4H, J = 4.9 Hz), 2.88-2.93 (m, 4H), 3.68 (t, 4H, J = 4.9 Hz), 7.18 (t, 1H, J = 2.4 Hz), 7.27 (s, 1H), 7.31-7.39 (m, 3H), 7.42 (dd, 1H, J = 8.2 Hz, 2 Hz), 7.53-7.59 (m, 3H), 8.49 (s, 1H), 10.412 (s, 1H). Mass spectrum, M + 1 = 562.

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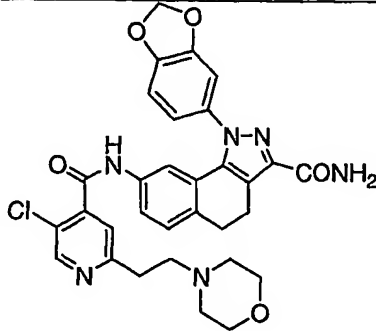
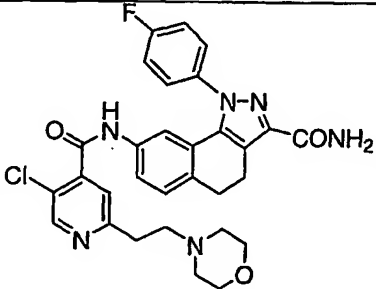
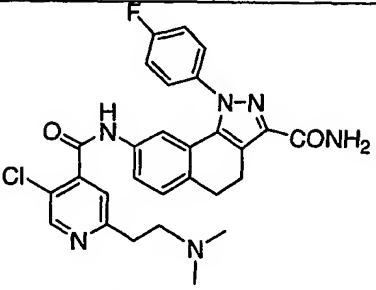
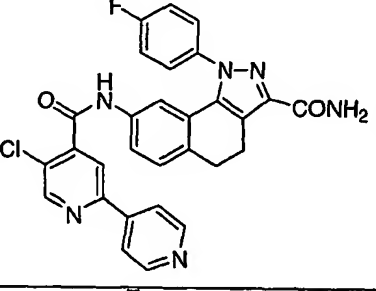
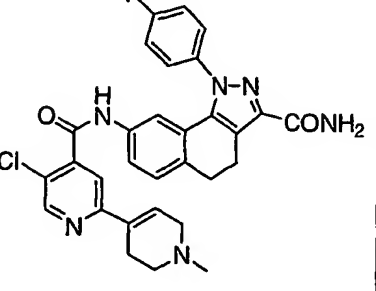
[00341] The bioactivity in the IKK2 Resin assay for the compounds of Examples 452-480 is shown in Table 24

Table 24

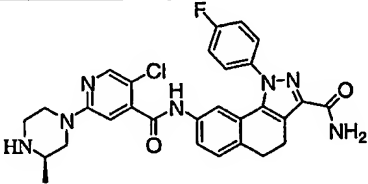
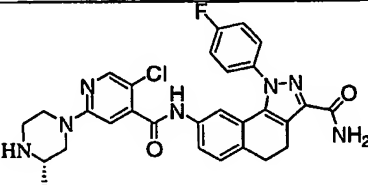
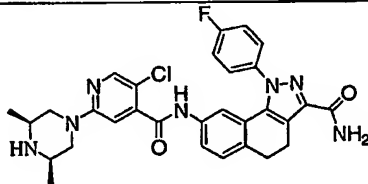
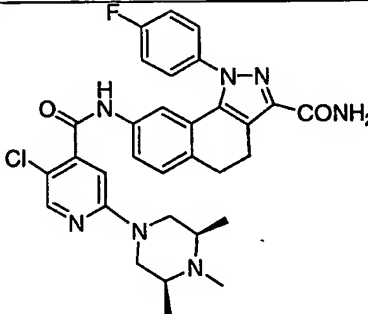
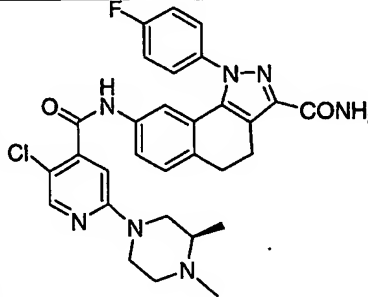
Compound No., Structure	Compound Name	IKK2 Resin IC <sub>50</sub>	Example
	8-[(2,5-Dichloroisonicotinoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	453 step 1
	8-[[5-Chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	453
	1-(1,3-Benzodioxol-5-yl)-8-[[[(6-chloro-4-methylpyridin-3-yl)carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	454
	1-(1,3-Benzodioxol-5-yl)-8-[[[(3-chloro-6-cyanopyridin-2-yl)carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	455 step 1
	8-[[[6-(Aminomethyl)-3-chloropyridin-2-yl]carbonyl]amino]-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	1 ≤ 10 μM	455

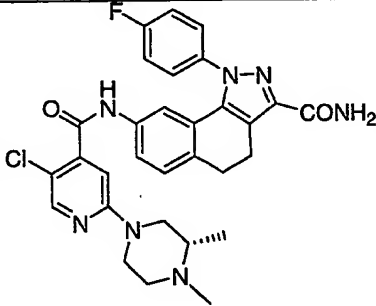
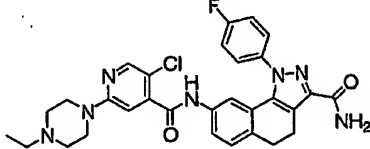
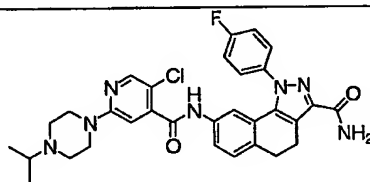
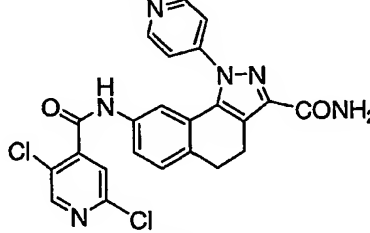
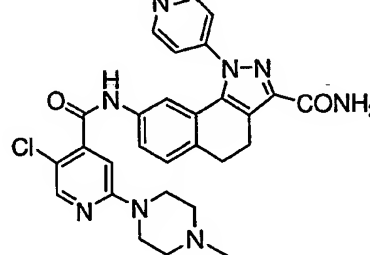
Compound No., Structure	Compound Name	IKK2 Resin IC50	Example
	8-[(5-Chloro-2-cyanoisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	456 step 1
	8-[[2-(Aminomethyl)-5-chloroisonicotinoyl]amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	456
	1-(1,3-Benzodioxol-5-yl)-8-[(5-chloro-2-cyanoisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	457 step 1
	8-[[2-(Aminomethyl)-5-chloroisonicotinoyl]amino]-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	457
	8-([3-Chloro-6-(morpholin-4-ylmethyl)pyridin-2-yl]carbonyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamid	$\leq 1 \mu\text{M}$	458
	1-(1,3-Benzodioxol-5-yl)-8-([3-chloro-6-(morpholin-4-ylmethyl)pyridin-2-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	459

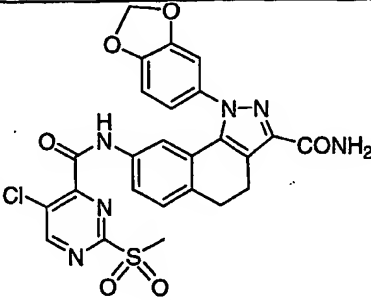
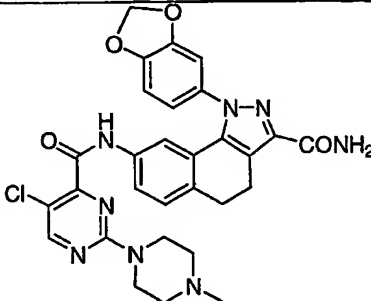
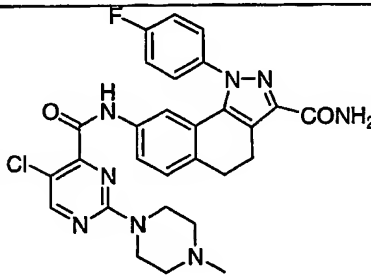


Compound No., Structure	Compound Name	IKK2 Resin IC <sub>50</sub>	Example
	1-(1,3-Benzodioxol-5-yl)-8-([5-chloro-2-(2-morpholin-4-ylethyl)isonicotinoyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	460
	8-([5-Chloro-2-(2-morpholin-4-ylethyl)isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	461
	8-([5-Chloro-2-[2-(dimethylamino)ethyl]isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	462
	8-([(5-Chloro-2,4'-bipyridin-4-yl)carbonyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	463
	8-([(5-chloro-1'-methyl-1',2',3',6'-tetrahydro-2,4'-bipyridin-4-yl)carbonyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	464

Compound No., Structure	Compound Name	IKK2 Resin IC50	Example
	1-(4-Fluorophenyl)-8-[(2-morpholin-4-ylisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	465
	8-[(5-chloro-2-(1,4-diazepan-1-yl)isonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	466
	8-[(5-Chloro-2-[4-(2-hydroxyethyl)piperazin-1-yl]isonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	467
	8-[(5-Chloro-2-[4-(2-methoxyethyl)piperazin-1-yl]isonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	468
	8-[(5-Chloro-2-[(2-(dimethylamino)ethyl)amino]isonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	≤1 μM	469

Compound No., Structure	Compound Name	IKK2 Resin IC50	Example
	8-((5-Chloro-2-[(3R)-3-methylpiperazin-1-yl]isonicotinoyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	470
	8-((5-Chloro-2-[(3S)-3-methylpiperazin-1-yl]isonicotinoyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	471
	8-((5-Chloro-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]isonicotinoyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	472
	8-((5-Chloro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]isonicotinoyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	473
	8-((5-Chloro-2-[(3R)-3,4-dimethylpiperazin-1-yl]isonicotinoyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	474

Compound No., Structure	Compound Name	IKK2 Resin IC50	Example
	8-((5-Chloro-2-((3S)-3,4-dimethylpiperazin-1-yl)isonicotinoyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	475
	8-([5-Chloro-2-(4-ethylpiperazin-1-yl)isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	476
	8-([5-Chloro-2-(4-isopropylpiperazin-1-yl)isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	477
	8-((2,5-Dichloroisonicotinoyl)amino)-1-pyridin-4-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	478 step 1
	8-([5-Chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino)-1-pyridin-4-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	478

Compound No., Structure	Compound Name	IKK2 Resin IC50	Example
	1-(1,3-Benzodioxol-5-yl)-8-([5-chloro-2-(methylsulfonyl)pyrimidin-4-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	479 step 2
	1-(1,3-Benzodioxol-5-yl)-8-([5-chloro-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	479
	8-([5-Chloro-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]carbonyl)amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide	$\leq 1 \mu\text{M}$	480

## BIOLOGICAL EVALUATION

### 5 Materials

[00342] SAM<sup>2</sup>™ 96 Biotin capture plates were from Promega. Anti-FLAG affinity resin, FLAG-peptide, NP-40 (Nonidet P-40), BSA, ATP, ADP, AMP, LPS (*E. coli* serotype 0111:B4), and dithiothreitol were obtained from Sigma Chemicals. Antibodies specific for NEMO (IKK $\gamma$ ) (FL-419), IKK1(H-744), IKK2(H-470) and IkB $\alpha$ (C-21) were purchased from Santa Cruz Biotechnology. Ni-NTA resin was purchased from Qiagen. Peptides were purchased from American Peptide Company. Protease inhibitor cocktail tablets were from Boehringer Mannheim.

Sephacryl S-300 column was from Pharmacia LKB Biotechnology. Centriprep-10 concentrators with a molecular weight cutoff of 10 kDa and membranes with molecular weight cut-off of 30 kDa were obtained from Amicon. [ $\gamma$ - $^{33}\text{P}$ ] ATP (2500 Ci/mmol) and [ $\gamma$ - $^{32}\text{P}$ ] ATP (6000 Ci/mmol) were purchased from Amersham.

5 The other reagents used were of the highest grade commercially available.

#### *Cloning and Expression*

[00343] cDNAs of human IKK1 and IKK2 were amplified by reverse transcriptase-polymerase chain reaction from human placental RNA (Clontech).

10 hIKK1 was subcloned into pFastBac HTa (Life Technologies) and expressed as N-terminal His<sub>6</sub>-tagged fusion protein. The hIKK2 cDNA was amplified using a reverse oligonucleotide primer which incorporated the peptide sequence for a FLAG-epitope tag at the C-terminus of the IKK2 coding region (DYKDDDDKD). The hIKK2:FLAG cDNA was subcloned into the baculovirus vector pFastBac. The

15 rhIKK2 (S177S, E177E) mutant was constructed in the same vector used for wild type rhIKK2 using a QuikChange<sup>TM</sup> mutagenesis kit (Stratagene). Viral stocks of each construct were used to infect insect cells grown in 40L suspension culture. The cells were lysed at a time that maximal expression and rhIKK activity were demonstrated. Cell lysates were stored at -80 °C until purification of the

20 recombinant proteins was undertaken as described below.

#### *Enzyme Isolation*

[00344] All purification procedures were carried out at 4 °C unless otherwise noted. Buffers used are: buffer A: 20 mM Tris-HCl, pH 7.6, containing 50 mM

25 NaCl, 20 mM NaF, 20 mM  $\beta$ -Glycerophosphate, 500  $\mu\text{M}$  sodiumortho-vanadate, 2.5 mM metabisulfite, 5 mM benzamidine, 1 mM EDTA, 0.5 mM EGTA, 10% glycerol, 1 mM DTT, 1X Complete<sup>TM</sup> protease inhibitors; buffer B: same as buffer A, except 150 mM NaCl, and buffer C: same as buffer A, except 500 mM NaCl.

#### *Isolation of rhIKK1 homodimer*

[00345] Cells from an 8-liter fermentation of baculovirus-expressed IKK1 tagged with His peptide were centrifuged and the cell pellet (MOI 0.1, I=72 hr) was

re-suspended in 100 ml of buffer C. The cells were microfluidized and centrifuged at 100,000 X g for 45 min. The supernatant was collected, imidazole added to the final concentration of 10 mM and incubated with 25 ml of Ni-NTA resin for 2 hrs. The suspension was poured into a 25 ml column and washed with 250 ml of buffer C and then with 125 ml of 50 mM imidazole in buffer C. rhIKK1 homodimer was eluted using 300 mM imidazole in buffer C. BSA and NP-40 were added to the enzyme fractions to the final concentration of 0.1 %. The enzyme was dialyzed against buffer B, aliquoted and stored at -80 °C.

10 *Isolation of rhIKK2 homodimer*

[00346] A 10-liter culture of baculovirus-expressing IKK2 tagged with FLAG peptide was centrifuged and the cell pellet (MOI=0.1 and I=72 hrs) was re-suspended in buffer A. These cells were microfluidized, and centrifuged at 100,000 X g for 45 min. Supernatant was passed over a G-25 column equilibrated with Buffer A. Protein peak was collected and incubated with anti-FLAG affinity resin on a rotator overnight in buffer B. The resin was washed in batch with 10-15 bed volumes of buffer C. Washed resin was poured into a column and rhIKK2 homodimer was eluted using 5 bed volumes of buffer B containing FLAG peptide. 5 mM DTT, 0.1% NP-40 and BSA (concentrated to 0.1% in final amount) was added to the eluted enzyme before concentrating in using an Amicon membrane with a molecular weight cut-off of 30 kDa. Enzyme was aliquoted and stored at -80 °C.

*Isolation of rhIKK1/IKK2 heterodimer*

25 [00347] The heterodimer enzyme was produced by coinfection in a baculovirus system (FLAG IKK2/IKK1 His; MOI=0.1 and I=72 hrs). Infected cells were centrifuged and the cell pellet (10.0 g) was suspended in 50 ml of buffer A. The protein suspension was microfluidized and centrifuged at 100,000 X g for 45 min. Imidazole was added to the supernatant to a final concentration of 10 mM. The protein was allowed to bind 25 ml of Ni-NTA resin by mixing for 2 hrs. The protein-resin slurry was poured into a 25 ml column and washed with 250 ml of buffer A containing 10 mM imidazole followed by 125 ml of buffer A containing

50 mM imidazole. Buffer A, containing 300 mM imidazole, was then used to elute the protein. A 75 ml pool was collected and NP-40 was added to a final concentration of 0.1%. The protein solution was then dialyzed against buffer B. The dialyzed heterodimer enzyme was then allowed to bind to 25 ml of anti-FLAG  
5 M2 agarose affinity gel overnight with constant mixing. The protein-resin slurry was then centrifuged for 5 min at 2,000 rpm. The supernatant was collected and the resin re-suspended in 100 ml of buffer C containing 0.1% NP-40. The resin was washed with 375 ml of buffer C containing 0.1 % NP-40. The protein-resin was poured into a 25 ml column and the enzyme eluted using buffer B containing FLAG  
10 peptide. Enzyme fractions (100 ml) were collected and concentrated to 20 ml using an Amicon membrane with molecular weight cut-off of 30 kDa. Bovine serum albumin was added to the concentrated enzyme to final concentration of 0.1 %. The enzyme was then aliquoted and stored at -80 °C.

#### 15 *Cell Culture*

[00348] The wild type (wt) human pre-B cell line, 70Z/3, and its mutant, 1.3E2, were generously provided by Dr. Carol Sibley. Wt 70Z/3 and 1.3E2 cells were grown in RPMI 1640 (Gibco) supplemented with 7 % defined bovine serum (Hyclone) and 50 µM 2-mercaptoethanol. Human monocytic leukemia THP-1 cells,  
20 obtained from ATCC, were cultured in RPMI 1640 supplemented with 10% defined bovine serum, 10 mM HEPES, 1.0 mM sodium pyruvate and 50 µM 2-mercaptoethanol. For experiments, cells were plated in 6 well plates at  $1 \times 10^6$  cells/ml in fresh media. Pre-B cells were stimulated by the addition of 10 µg/ml LPS for varying lengths of time ranging from 0-4 hr. THP-1 cells were stimulated  
25 by the addition of 1 µg/ml LPS for 45 minutes. Cells were pelleted, washed with cold 50 mM sodium phosphate buffer, pH 7.4 containing 0.15 M NaCl and lysed at 4 °C in 20 mM Hepes buffer, pH 7.6 containing 50 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM sodium orthovanadate, 10 mM β-glycerophosphate, 1 mM NaF, 1 mM PMSF, 1 mM DTT and 0.5 % NP40 (lysis buffer). The cytosolic fractions  
30 obtained following centrifugation at 10,000 X g were stored at -80° C until used.



*Immunoprecipitation and Western Blotting*

[00349] SF9 cells paste containing rhIKKs were centrifuged (100,000 X g, 10 min) to remove debris. rhIKKs were immunoprecipitated (100 µg of cell paste) from the cell supernatant using 3 µg of anti-NEMO antibody (FL-419), followed by coupling to protein A sepharose beads. rhIKKs were also immunoprecipitated from affinity chromatography purified protein preparations (1 µg) using anti-FLAG, anti-His or anti-NEMO antibodies (1-4 µg) followed by protein A sepharose coupling. The native, human IKK complex was immunoprecipitated from THP-1 cell homogenates (300 µg/condition) using the anti-NEMO antibody. Immune complexes were pelleted and washed 3 times with 1 ml cold lysis buffer. Immunoprecipitated rhIKKs were chromatographed by SDS-PAGE (8% Tris-glycine) and transferred to nitrocellulose membranes (Novex) and detected by chemiluminescence (SuperSignal) using specific anti-IKK antibodies (IKK2 H-470, IKK1 H-744). Native IKK2, IκBα, and NEMO proteins from cytosolic lysates (20-80 µg) were separated by SDS-PAGE and visualized by chemiluminescence using specific antibodies.

*Phosphatase Treatment*

[00350] Immunoprecipitated rhIKKs were washed 2 times in 50 mM Tris-HCl, pH 8.2 containing 0.1 mM EDTA, 1 mM DTT, 1 mM PMSF and 2 mM MnCl<sub>2</sub> and resuspended in 50 µl. Phosphatase (λPPase, 1000 U) was pre-diluted in the same buffer and added to the IKK samples. Following an incubation at room temperature for 30 minutes with intermittent mixing, cold lysis buffer was added to the tubes to stop the reaction. After several washes, 10 % of the beads were removed for Western analysis, and the remaining material was pelleted and resuspended in 100 µl of the buffer used for the *in vitro* kinase assay.

*IKKα SAM Enzyme Assay*

[00351] IKKα kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser<sub>32</sub>-Gly-Leu-

Asp-Ser<sub>36</sub>-Met-Lys-Asp-Glu-Glu), a SAM<sup>2</sup>™ 96 Biotin capture plate and a vacuum system. The standard reaction mixture contained 5 μM biotinylated IκBα peptide, 1 μM [ $\gamma$ -<sup>33</sup>P] ATP (about 1 X 10<sup>5</sup> cpm), 1 mM DTT, 50 mM KCl, 2 mM MgCl<sub>2</sub>, 2 mM MnCl<sub>2</sub>, 10 mM NaF, 25 mM Hepes buffer, pH. 7.6 and enzyme solution (1-10 μl) in a final volume of 50 μl. After incubation at 25 °C for 30 min, 25 μl of the reaction mixture was withdrawn and added to a SAM<sup>2</sup>™ 96 Biotin capture 96-well plate. Each well was then washed successively with 800 μl 2 M NaCl, 1.2 ml of NaCl containing 1% H<sub>3</sub>PO<sub>4</sub>, 400 μl H<sub>2</sub>O, and 200 μl 95% ethanol. The plate was allowed to dry in a hood at 25 °C for 1 hr and then 25 μl of scintillation fluid (Microscint 20) was added to each well. Incorporation of [ $\gamma$ -<sup>33</sup>P] ATP was measured using a Top-Count NXT (Packard). Under each assay condition, the degree of phosphorylation of IκBα peptide substrate was linear with time and concentration for all purified enzymes. Results from the biotinylated peptide assay were confirmed by SDS-PAGE analysis of kinase reaction utilizing a GST-IκBα<sub>1-54</sub> and [ $\gamma$ -<sup>32</sup>P] ATP. The resulting radiolabeled substrate was quantitated by Phosphoimager (Molecular Dynamics). An ion exchange resin assay was also employed using [ $\gamma$ -<sup>33</sup>P] ATP and GST-IκBα<sub>1-54</sub> fusion protein as the substrates. Each assay system yielded consistent results in regard to K<sub>m</sub> and specific activities for each of the purified kinase isoforms. One unit of enzyme activity was defined as the amount required to catalyze the transfer of 1 nmole of phosphate from ATP to IκBα peptide per min. Specific activity was expressed as units per mg of protein. For experiments related to K<sub>m</sub> determination of purified enzymes, various concentrations of ATP or IκBα peptide were used in the assay at either a fixed IκBα or ATP concentration. For IκBα peptide K<sub>m</sub>, assays were carried out with 0.1 μg of enzyme, 5 μM ATP and IκBα peptide from 0.5 to 20 μM. For ATP K<sub>m</sub>, assays were carried out with 0.1 μg of enzyme, 10 μM IκBα peptide and ATP from 0.1 to 10 μM. For K<sub>m</sub> determination of rhIKK1 homodimer, due to its low activity and higher K<sub>m</sub> for IκBα peptide, rhIKK1 homodimer (0.3 μg) was assayed with 125 μM IκBα peptide and a 5-fold higher specific activity of ATP (from 0.1 to 10 μM) for ATP K<sub>m</sub> experiments and a 5-fold higher specific activity of 5 μM ATP and IκBα peptide (from 5 to 200 μM) for IκBα peptide K<sub>m</sub> experiments.

*IKK $\beta$  Resin Enzyme Assay*

[00352] IKK $\beta$  kinase activity was measured using a biotinylated IkB $\alpha$  peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser<sub>32</sub>-Gly-Leu-Asp-Ser<sub>36</sub>-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20  $\mu$ l of the standard  
5 reaction mixture contained 5  $\mu$ M biotinylated IkB $\alpha$  peptide, 0.1  $\mu$ Ci/reaction [ $\gamma$ -<sup>33</sup>P] ATP (Amersham) (about 1 X 10<sup>5</sup> cpm), 1  $\mu$ M ATP (Sigma), 1 mM DTT (Sigma), 2 mM MgCl<sub>2</sub> (Sigma), 2 mM MnCl<sub>2</sub> (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20  $\mu$ l enzyme solution and 10  $\mu$ l inhibitor in a final  
10 volume of 50  $\mu$ l. After incubation at 25 °C for 30 min, 150  $\mu$ l resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was allowed to settle for one hour and 50  $\mu$ l of supernatant was removed to a Microlite-2 flat bottom plate (Dynex). 150  $\mu$ l of scintillation fluid (Microscint 40) (Packard) was added to each well. Incorporation  
15 of [ $\gamma$ -<sup>33</sup>P] ATP was measured using a Top-Count NXT (Packard).

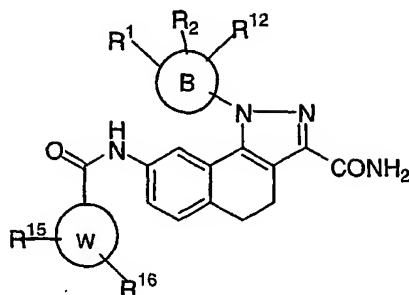
*IKK heterodimer Resin Enzyme Assay*

[00353] IKK heterodimer kinase activity was measured using a biotinylated IkB $\alpha$  peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser<sub>32</sub>-Gly-Leu-Asp-Ser<sub>36</sub>-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20  $\mu$ l of the  
20 standard reaction mixture contained 5  $\mu$ M biotinylated IkB $\alpha$  peptide, 0.1  $\mu$ Ci/reaction [ $\gamma$ -<sup>33</sup>P] ATP (Amersham) (about 1 X 10<sup>5</sup> cpm), 1  $\mu$ M ATP (Sigma), 1 mM DTT (Sigma), 2 mM MgCl<sub>2</sub> (Sigma), 2 mM MnCl<sub>2</sub> (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20  $\mu$ l enzyme solution and 10  $\mu$ l  
25 inhibitor in a final volume of 50  $\mu$ l. After incubation at 25 °C for 30 min, 150  $\mu$ l resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was allowed to settle for one hour and 50  $\mu$ l of supernatant was removed to a Microlite-2 flat bottom plate  
(Dynex). 150  $\mu$ l of scintillation fluid (Microscint 40) (Packard) was added to each  
30 well. Incorporation of [ $\gamma$ -<sup>33</sup>P] ATP was measured using a Top-Count NXT (Packard).

## WHAT IS CLAIMED IS:

1. The compound of Formula III

5



wherein

10 B is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic wherein said aryl, heteroaryl, or heterocyclic are optionally substituted with  $R^1$ ,  $R^2$ , and  $R^{12}$ ;

W is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic;

15  $R^1$  is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN,  $NO_2$ ,  $OR^5$ ,  $OCOOR^5$ ,  $CO_2R^7$ ,  $CON(R^6)R^7$ ,  $COR^6$ ,  $SR^6$ ,  $SOR^6$ ,  $SO_2R^6$ ,  $NR^6R^7$ ,  $NR^6COR^7$ ,  $NR^6CONHR^7$ ,  $NR^6SO_2R^7$ ,  $NR^6SO_2NHR^7$ , and  $SO_2N(R^6)R^7$  wherein  $R^6$  and  $R^7$  may be taken together to form a 3-7

20 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO,  $SO_2$ , O, and  $NR^6$ ; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or  $OR^5$  are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl,  $COCF_3$ , CN,  $NO_2$ ,  $OR^5$ ,  $OCOOR^5$ ,  $CO_2R^7$ ,  $CON(R^6)R^7$ ,  $COR^6$ ,  $SR^6$ ,  $SOR^6$ ,  $SO_2R^6$ ,  $NR^6R^7$ ,  $NR^6COR^7$ ,  $NR^6CONHR^7$ ,  $NR^6SO_2R^7$ ,  $NR^6SO_2NHR^7$ , and  $SO_2N(R^6)R^7$  wherein

25  $R^6$  and  $R^7$  may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted

- heteroatoms selected from the group consisting of: S, SO, SO<sub>2</sub>, O, and NR<sup>6</sup>;
- R<sup>2</sup> is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl, OR<sup>6</sup>, CN, NO<sub>2</sub>, SR<sup>6</sup>, NHR<sup>6</sup>, CON(R<sup>6</sup>)R<sup>7</sup>, NHCONHR<sup>6</sup>, CO<sub>2</sub>H, and haloalkyl;
- R<sup>1</sup> and R<sup>2</sup> may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of N, O, or S, and wherein said ring is optionally substituted with R<sup>1</sup>;
- R<sup>5</sup> is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of OR<sup>14</sup>, N(R<sup>14</sup>)R<sup>14'</sup>, and glycols;
- R<sup>6</sup> is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;
- R<sup>7</sup> is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;
- R<sup>12</sup> is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;
- R<sup>15</sup> is selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl wherein said alkyl is optionally substituted with a carbocyclic or heterocyclic wherein said carbocyclic or heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is

optionally substituted with one or more halogen,  $(\text{CH}_2)_n\text{C}(\text{R}')\text{R}'$  wherein  $n$  is 0 to 4 and each  $\text{R}'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(\text{CH}_2)_n\text{NHCON}(\text{R}')\text{R}'$  wherein  $n$  is 0 to 4 and each  $\text{R}'$  is

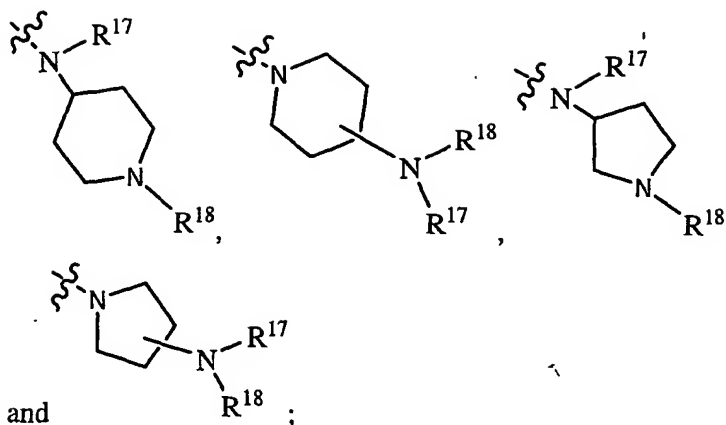
5 independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(\text{CH}_2)_n\text{NHC}(\text{O})\text{OR}'$  wherein  $n$  is 0 to 4 and  $\text{R}'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl; alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, halogen,

10 acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkylendioxy, hydroxyalkyl, alkylamino, alkylloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl,

15 alkynyl, dialkylaminoalkyloxy, and heterocyclic wherein said heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy,

20 alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(\text{CH}_2)_n\text{C}(\text{R}')\text{R}'$  wherein  $n$  is 0 to 4 and each  $\text{R}'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(\text{CH}_2)_n\text{NHCON}(\text{R}')\text{R}'$  wherein  $n$  is

25 0 to 4 and each  $\text{R}'$  is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(\text{CH}_2)_n\text{NHC}(\text{O})\text{OR}'$  wherein  $n$  is 0 to 4 and  $\text{R}'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl,



$R^{17}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl; and

$R^{18}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl;

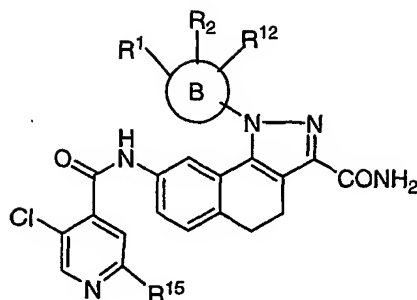
or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

2. The compound of claim 1,

wherein

$R^{16}$  is selected from the group consisting of: hydrido, halogen, and lower alkyl.

3. The compound of claim 2 of the Formula



wherein

B is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic wherein said aryl, heteroaryl, or heterocyclic are optionally substituted with  $R^1$ ,  $R^2$ , and  $R^{12}$ ;

$R^1$  is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN,  $NO_2$ ,  $OR^5$ ,  $OCOOR^5$ ,  $CO_2R^7$ ,  $CON(R^6)R^7$ ,  $COR^6$ ,  $SR^6$ ,  $SOR^6$ ,  $SO_2R^6$ ,  $NR^6R^7$ ,  $NR^6COR^7$ ,  $NR^6CONHR^7$ ,  $NR^6SO_2R^7$ ,  $NR^6SO_2NHR^7$ , and  $SO_2N(R^6)R^7$  wherein  $R^6$  and  $R^7$  may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO,  $SO_2$ , O, and  $NR^6$ ; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or  $OR^5$  are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl,  $COCF_3$ , CN,  $NO_2$ ,  $OR^5$ ,  $OCOOR^5$ ,  $CO_2R^7$ ,  $CON(R^6)R^7$ ,  $COR^6$ ,  $SR^6$ ,  $SOR^6$ ,  $SO_2R^6$ ,  $NR^6R^7$ ,  $NR^6COR^7$ ,  $NR^6CONHR^7$ ,  $NR^6SO_2R^7$ ,  $NR^6SO_2NHR^7$ , and  $SO_2N(R^6)R^7$  wherein  $R^6$  and  $R^7$  may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO,  $SO_2$ , O, and  $NR^6$ ;

$R^2$  is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl,  $OR^6$ , CN,  $NO_2$ ,  $SR^6$ ,  $NHR^6$ ,  $CON(R^6)R^7$ ,  $NHCONHR^6$ ,  $CO_2H$ , and haloalkyl;

$R^1$  and  $R^2$  may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3



heteroatoms selected from the group consisting of N, O, or S, and wherein said ring is optionally substituted with R<sup>1</sup>;

R<sup>5</sup> is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of OR<sup>14</sup>, N(R<sup>14</sup>)R<sup>14'</sup>, and glycols;

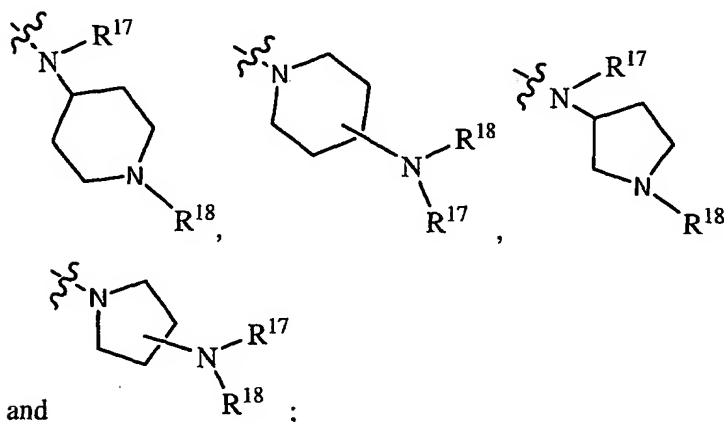
R<sup>6</sup> is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R<sup>7</sup> is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R<sup>12</sup> is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;

R<sup>15</sup> is selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl wherein said alkyl is optionally substituted with a carbocyclic or heterocyclic wherein said carbocyclic or heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen, (CH<sub>2</sub>)<sub>n</sub>C(R')R' wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl, (CH<sub>2</sub>)<sub>n</sub>NHCON(R')R' wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl, (CH<sub>2</sub>)<sub>n</sub>NHC(O)OR' wherein n is 0 to 4 and R' is selected from the group consisting of hydrido, hydroxy,

amino, and alkyl; alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino,  
 aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, halogen,  
 acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl,  
 hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy,  
 5 dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate,  
 isothiocyanate, alkylendioxy, hydroxyalkyl, alkylamino,  
 alkylloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl,  
 alkynyl, dialkylaminoalkyloxy, and heterocyclic wherein said  
 heterocyclic is optionally substituted with one to six substituents  
 10 selected from the group consisting of alkyl, alkylamino, aminoalkyl,  
 hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino,  
 dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy,  
 alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl,  
 heteroaryl wherein said heteroaryl is optionally substituted with one  
 15 or more halogen,  $(CH_2)_n C(R')R'$  wherein  $n$  is 0 to 4 and each  $R'$  is  
 independently selected from the group consisting of hydrido,  
 hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein  $n$  is  
 0 to 4 and each  $R'$  is independently selected from the group  
 consisting of hydrido, hydroxy, amino, and alkyl,  
 20  $(CH_2)_n NHC(O)OR'$  wherein  $n$  is 0 to 4 and  $R'$  is selected from the  
 group consisting of hydrido, hydroxy, amino, and alkyl,



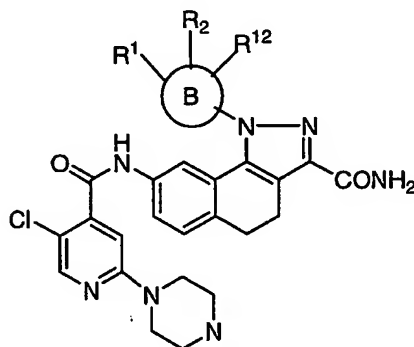
25  $R^{17}$  is selected from the group consisting of: alkyl, hydroxyalkyl,  
 alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl,

alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl; and

5  $R^{18}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

15 4. The compound of claim 3 of the Formula



wherein

20 B is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic wherein said aryl, heteroaryl, or heterocyclic are optionally substituted with  $R^1$ ,  $R^2$ , and  $R^{12}$ ;

$R^1$  is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN, NO<sub>2</sub>, OR<sup>5</sup>,  
 25 OCOOR<sup>5</sup>, CO<sub>2</sub>R<sup>7</sup>, CON(R<sup>6</sup>)R<sup>7</sup>, COR<sup>6</sup>, SR<sup>6</sup>, SOR<sup>6</sup>, SO<sub>2</sub>R<sup>6</sup>, NR<sup>6</sup>R<sup>7</sup>, NR<sup>6</sup>COR<sup>7</sup>, NR<sup>6</sup>CONHR<sup>7</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>6</sup>SO<sub>2</sub>NHR<sup>7</sup>, and

- 5  $\text{SO}_2\text{N}(\text{R}^6)\text{R}^7$  wherein  $\text{R}^6$  and  $\text{R}^7$  may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO,  $\text{SO}_2$ , O, and  $\text{NR}^6$ ; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or  $\text{OR}^5$  are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl,  $\text{COCF}_3$ , CN,  $\text{NO}_2$ ,  $\text{OR}^5$ ,  $\text{OCOOR}^5$ ,  $\text{CO}_2\text{R}^7$ ,  $\text{CON}(\text{R}^6)\text{R}^7$ ,  $\text{COR}^6$ ,  $\text{SR}^6$ ,  $\text{SOR}^6$ ,  $\text{SO}_2\text{R}^6$ ,  $\text{NR}^6\text{R}^7$ ,  $\text{NR}^6\text{COR}^7$ ,  $\text{NR}^6\text{CONHR}^7$ ,  $\text{NR}^6\text{SO}_2\text{R}^7$ ,  $\text{NR}^6\text{SO}_2\text{NHR}^7$ , and  $\text{SO}_2\text{N}(\text{R}^6)\text{R}^7$  wherein  $\text{R}^6$  and  $\text{R}^7$  may be taken together to form a 3-7 membered
- 10 carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO,  $\text{SO}_2$ , O, and  $\text{NR}^6$ ;
- $\text{R}^2$  is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl,  $\text{OR}^6$ , CN,  $\text{NO}_2$ ,  $\text{SR}^6$ ,  $\text{NHR}^6$ ,  $\text{CON}(\text{R}^6)\text{R}^7$ ,
- 15  $\text{NHCONHR}^6$ ,  $\text{CO}_2\text{H}$ , and haloalkyl;
- $\text{R}^1$  and  $\text{R}^2$  may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of N, O, or S, and wherein said ring is optionally substituted with  $\text{R}^1$ ;
- 20  $\text{R}^5$  is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of  $\text{OR}^{14}$ ,  $\text{N}(\text{R}^{14})\text{R}^{14'}$ , and glycols;
- 25  $\text{R}^6$  is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;
- $\text{R}^7$  is independently selected from the group consisting of: hydrido,
- 30 aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

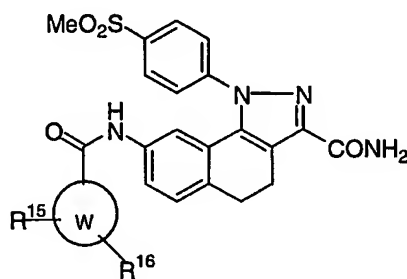
$R^{12}$  is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;

5 wherein the piperazine is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one  
10 or more halogen,  $(CH_2)_n C(R')R'$  wherein  $n$  is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein  $n$  is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  
15  $(CH_2)_n NHC(O)OR'$  wherein  $n$  is 0 to 4 and  $R'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

20

5. The compound of claim 1 of the Formula



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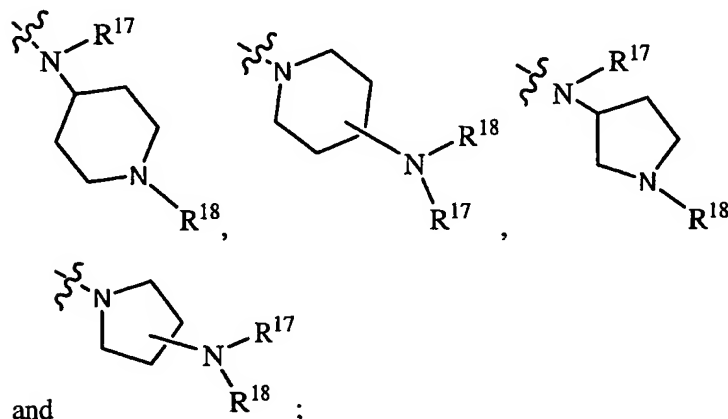
wherein

W is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic;

$R^{15}$  is selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl wherein said alkyl is optionally substituted with a carbocyclic or heterocyclic wherein said carbocyclic or heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(CH_2)_n C(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(CH_2)_n NHC(O)OR'$  wherein n is 0 to 4 and  $R'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl; alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkylldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic wherein said heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(CH_2)_n C(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein n is

0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl, (CH<sub>2</sub>)<sub>n</sub>NHC(O)OR' wherein n is 0 to 4 and R' is selected from the group consisting of hydrido, hydroxy, amino, and alkyl,

5



and

R<sup>17</sup> is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl; and

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R<sup>18</sup> is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl;

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or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

6. The compound of claim 5,

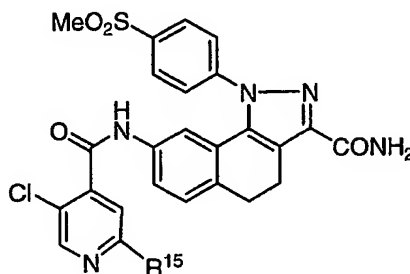
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wherein

$R^{16}$  is selected from the group consisting of: hydrido, halogen, and lower alkyl.

7. The compound of claim 6 of the Formula

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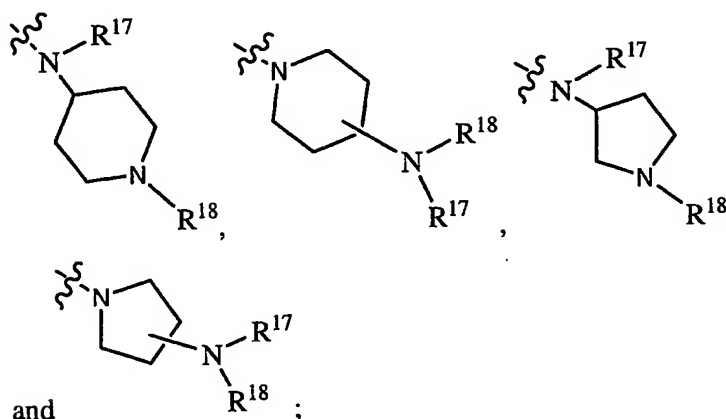


wherein

$R^{15}$  is selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl wherein said alkyl is optionally substituted with a carbocyclic or heterocyclic wherein said carbocyclic or heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(CH_2)_n C(R')R'$  wherein  $n$  is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein  $n$  is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(CH_2)_n NHC(O)OR'$  wherein  $n$  is 0 to 4 and  $R'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl; alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy,



dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate,  
 isothiocyanate, alkylidioxy, hydroxyalkyl, alkylamino,  
 alkylloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl,  
 alkynyl, dialkylaminoalkyloxy, and heterocyclic wherein said  
 5 heterocyclic is optionally substituted with one to six substituents  
 selected from the group consisting of alkyl, alkylamino, aminoalkyl,  
 hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino,  
 dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy,  
 alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl,  
 10 heteroaryl wherein said heteroaryl is optionally substituted with one  
 or more halogen,  $(CH_2)_n C(R')R'$  wherein  $n$  is 0 to 4 and each  $R'$  is  
 independently selected from the group consisting of hydrido,  
 hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein  $n$  is  
 0 to 4 and each  $R'$  is independently selected from the group  
 15 consisting of hydrido, hydroxy, amino, and alkyl,  
 $(CH_2)_n NHC(O)OR'$  wherein  $n$  is 0 to 4 and  $R'$  is selected from the  
 group consisting of hydrido, hydroxy, amino, and alkyl,



20  $R^{17}$  is selected from the group consisting of: alkyl, hydroxyalkyl,  
 alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl,  
 alkylsulfonyl, arylsulfonyl,  $CO(alkyl)$ ,  $CO(aryl)$ ,  $CO(CH_2)_n OH$  [ $n =$   
 0 to 4],  $CO_2(alkyl)$ ,  $CON(alkyl)(alkyl')$ , formyl, cycloalkyl,  
 25 heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl,  
 arylalkyl, and heteroarylalkyl; and

5  $R^{18}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

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8. The compound of claim 7 wherein  $R^{15}$  is piperazine attached at position 1 of the piperazine and said piperazine is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen, (CH<sub>2</sub>)<sub>n</sub>C(R')R' wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl, (CH<sub>2</sub>)<sub>n</sub>NHCON(R')R' wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl, (CH<sub>2</sub>)<sub>n</sub>NHC(O)OR' wherein n is 0 to 4 and R' is selected from the group consisting of hydrido, hydroxy, amino, and alkyl.

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9. The compound of claim 7 or 8 selected from the group consisting of:

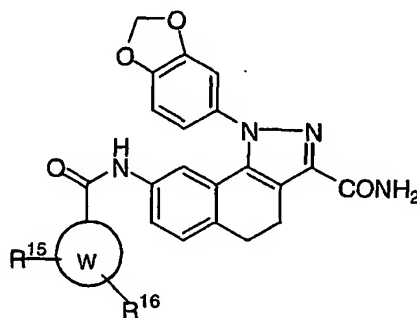
8-{{[5-Chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino}-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide, and

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8-[(2,5-Dichloroisonicotinoyl)amino]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide.

10. The compound of claim 1 of the Formula

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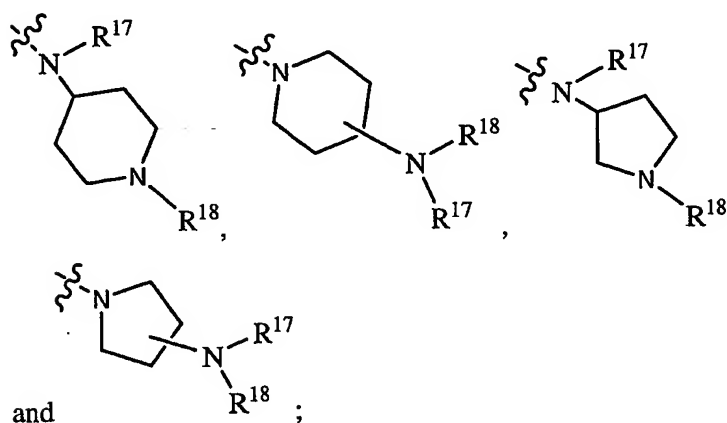


wherein

W is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic;

$R^{15}$  is selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl wherein said alkyl is optionally substituted with a carbocyclic or heterocyclic wherein said carbocyclic or heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(CH_2)_n C(R')R'$  wherein  $n$  is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein  $n$  is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(CH_2)_n NHC(O)OR'$  wherein  $n$  is 0 to 4 and  $R'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl; alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino,

aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkylendioxy, hydroxyalkyl, alkylamino, alkylloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic wherein said heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(\text{CH}_2)_n\text{C}(\text{R}')\text{R}'$  wherein  $n$  is 0 to 4 and each  $\text{R}'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(\text{CH}_2)_n\text{NHCON}(\text{R}')\text{R}'$  wherein  $n$  is 0 to 4 and each  $\text{R}'$  is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(\text{CH}_2)_n\text{NHC}(\text{O})\text{OR}'$  wherein  $n$  is 0 to 4 and  $\text{R}'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl,



$\text{R}^{17}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl,  $\text{CO}(\text{alkyl})$ ,  $\text{CO}(\text{aryl})$ ,  $\text{CO}(\text{CH}_2)_n\text{OH}$  [ $n =$

0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl; and

R<sup>18</sup> is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl;

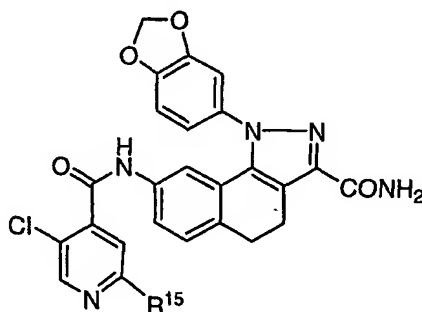
or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

11. The compound of claim 10,

wherein

R<sup>16</sup> is selected from the group consisting of: hydrido, halogen, and lower alkyl.

12. The compound of claim 11 of the Formula

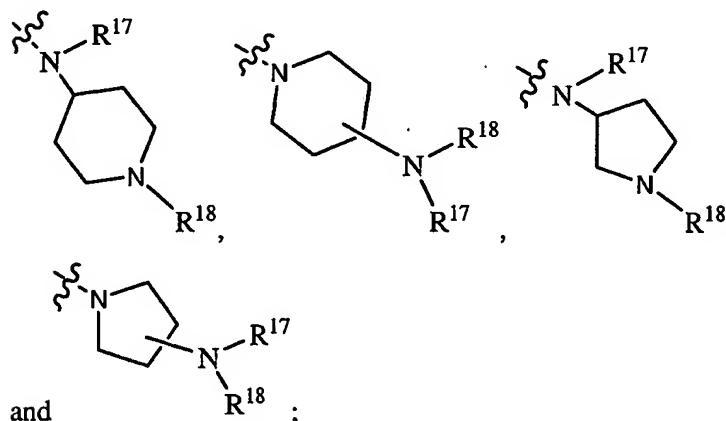


wherein

R<sup>15</sup> is selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl wherein said alkyl is optionally substituted with a

carbocyclic or heterocyclic wherein said carbocyclic or heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(\text{CH}_2)_n\text{C}(\text{R}')\text{R}'$  wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(\text{CH}_2)_n\text{NHCON}(\text{R}')\text{R}'$  wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(\text{CH}_2)_n\text{NHC}(\text{O})\text{OR}'$  wherein n is 0 to 4 and R' is selected from the group consisting of hydrido, hydroxy, amino, and alkyl; alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkylldioxy, hydroxyalkyl, alkylamino, alkylloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic wherein said heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(\text{CH}_2)_n\text{C}(\text{R}')\text{R}'$  wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(\text{CH}_2)_n\text{NHCON}(\text{R}')\text{R}'$  wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,

$(\text{CH}_2)_n\text{NHC(O)OR}'$  wherein  $n$  is 0 to 4 and  $\text{R}'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl,



$\text{R}^{17}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl,  $\text{CO}(\text{alkyl})$ ,  $\text{CO}(\text{aryl})$ ,  $\text{CO}(\text{CH}_2)_n\text{OH}$  [ $n = 0$  to 4],  $\text{CO}_2(\text{alkyl})$ ,  $\text{CON}(\text{alkyl})(\text{alkyl}')$ , formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl; and

$\text{R}^{18}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl,  $\text{CO}(\text{alkyl})$ ,  $\text{CO}(\text{aryl})$ ,  $\text{CO}(\text{CH}_2)_n\text{OH}$  [ $n = 0$  to 4],  $\text{CO}_2(\text{alkyl})$ ,  $\text{CON}(\text{alkyl})(\text{alkyl}')$ , formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

13. The compound of claim 10, 11, or 12 selected from the group consisting of:

1-(1,3-Benzodioxol-5-yl)-8-[[[(6-chloro-4-methylpyridin-3-yl)carbonyl]amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

8-([6-(Aminomethyl)-3-chloropyridin-2-yl]carbonyl)amino)-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

5 8-{[2-(Aminomethyl)-5-chloroisonicotinoyl]amino}-1-(1,3-benzodioxol-5-yl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

1-(1,3-Benzodioxol-5-yl)-8-([3-chloro-6-(morpholin-4-ylmethyl)pyridin-2-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

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1-(1,3-Benzodioxol-5-yl)-8-([5-chloro-2-(2-morpholin-4-ylethyl)isonicotinoyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

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1-(1,3-Benzodioxol-5-yl)-8-([3-chloro-6-cyanopyridin-2-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

1-(1,3-Benzodioxol-5-yl)-8-([5-chloro-2-cyanoisonicotinoyl]amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide, and

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1-(1,3-Benzodioxol-5-yl)-8-([5-chloro-2-(methylsulfonyl)pyrimidin-4-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide.

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14. The compound of claim 12 wherein R<sup>15</sup> is piperazine attached at position 1 of the piperazine and said piperazine is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen, (CH<sub>2</sub>)<sub>n</sub>C(R')R' wherein n is 0 to 4 and each R' is independently selected from the

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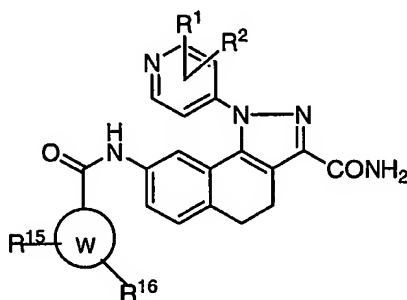


group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(\text{CH}_2)_n\text{NHCON}(\text{R}')\text{R}'$  wherein  $n$  is 0 to 4 and each  $\text{R}'$  is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(\text{CH}_2)_n\text{NHC}(\text{O})\text{OR}'$  wherein  $n$  is 0 to 4 and  $\text{R}'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl.

15. The compound of claim 14 selected from the group consisting of:

1-(1,3-Benzodioxol-5-yl)-8-([5-chloro-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]carbonyl)amino)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide.

16. The compound of claim 1 of the Formula



wherein

W is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic;

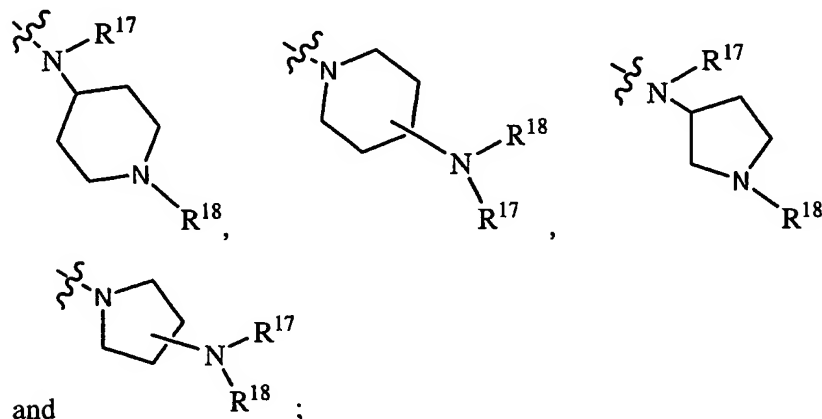
$\text{R}^1$  is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl,  $\text{OR}^6$ ,  $\text{CN}$ ,  $\text{SR}^6$ ,  $\text{NHR}^6$ ,  $\text{CON}(\text{R}^6)\text{R}^7$ ,  $\text{NHCONHR}^6$ , and haloalkyl;

$\text{R}^2$  is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl,  $\text{OR}^6$ ,  $\text{CN}$ ,  $\text{SR}^6$ ,  $\text{NHR}^6$ ,  $\text{CON}(\text{R}^6)\text{R}^7$ ,  $\text{NHCONHR}^6$ , and haloalkyl;

$R^{15}$  is selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl wherein said alkyl is optionally substituted with a carbocyclic or heterocyclic wherein said carbocyclic or heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(CH_2)_n C(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(CH_2)_n NHC(O)OR'$  wherein n is 0 to 4 and  $R'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl; alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkylldioxy, hydroxyalkyl, alkylamino, alkylloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic wherein said heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(CH_2)_n C(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein n is

0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl, (CH<sub>2</sub>)<sub>n</sub>NHC(O)OR' wherein n is 0 to 4 and R' is selected from the group consisting of hydrido, hydroxy, amino, and alkyl,

5



R<sup>17</sup> is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl; and

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R<sup>18</sup> is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl;

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or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

17. The compound of claim 16,

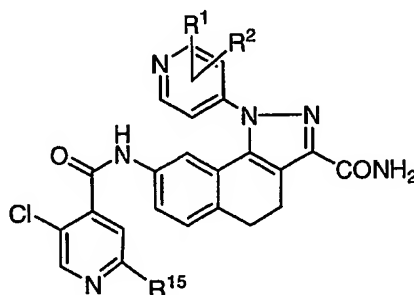
25

wherein

$R^2$  is selected from the group consisting of: hydrido and halogen;

$R^{16}$  is selected from the group consisting of: hydrido, halogen, and lower alkyl.

- 5                    18.    The compound of claim 17 of the Formula



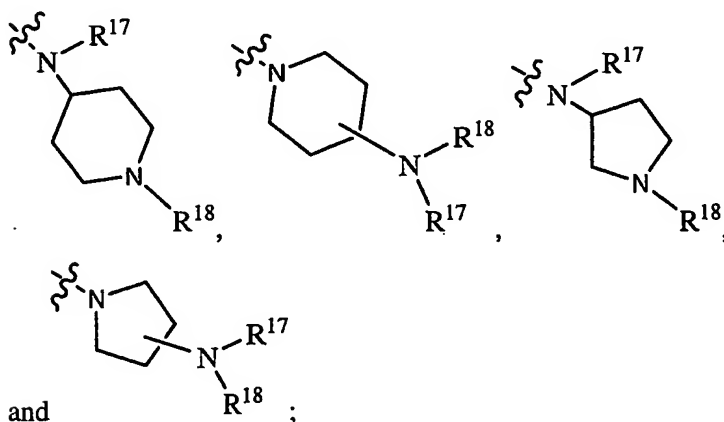
wherein

- 10                     $R^1$  is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl,  $OR^6$ , CN,  $SR^6$ ,  $NHR^6$ ,  $CON(R^6)R^7$ ,  $NHCONHR^6$ , and haloalkyl;

$R^2$  is selected from hydrido and halogen; and

- 15                     $R^{15}$  is selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl wherein said alkyl is optionally substituted with a carbocyclic or heterocyclic wherein said carbocyclic or heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, 20                    halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(CH_2)_n C(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl, 25                     $(CH_2)_n NHCON(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(CH_2)_n NHC(O)OR'$  wherein n is 0 to 4

and R' is selected from the group consisting of hydrido, hydroxy, amino, and alkyl; alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkylldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic wherein said heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(\text{CH}_2)_n\text{C}(\text{R}')\text{R}'$  wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  $(\text{CH}_2)_n\text{NHCON}(\text{R}')\text{R}'$  wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(\text{CH}_2)_n\text{NHC}(\text{O})\text{OR}'$  wherein n is 0 to 4 and R' is selected from the group consisting of hydrido, hydroxy, amino, and alkyl,



5  $R^{17}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl; and

10  $R^{18}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl;

15 or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

19. The compound of claim 18 wherein  $R^{15}$  is piperazine attached at position 1 of the piperazine wherein said piperazine is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen, (CH<sub>2</sub>)<sub>n</sub>C(R')R' wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl, (CH<sub>2</sub>)<sub>n</sub>NHCON(R')R' wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl, (CH<sub>2</sub>)<sub>n</sub>NHC(O)OR' wherein n is 0 to 4 and R' is selected from the group consisting of hydrido, hydroxy, amino, and alkyl.
- 20
- 25
- 30

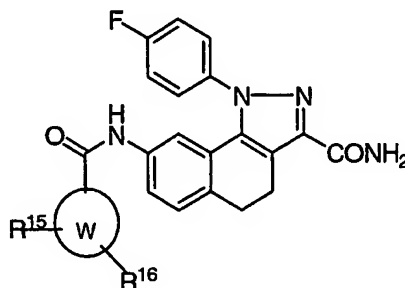
20. The compound of claim 18 or 19 selected from the group consisting of:

5 8-[[5-Chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino]-1-pyridin-4-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide, and

8-[(2,5-Dichloroisonicotinoyl)amino]-1-pyridin-4-yl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide.

10

21. The compound of claim 1 of the Formula



15

wherein

W is a 5 or 6 membered heteroaryl, aryl, saturated or unsaturated heterocyclic;

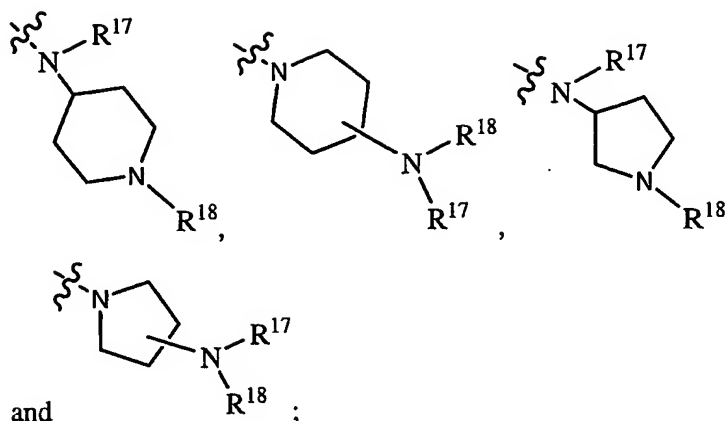
20

R<sup>15</sup> is selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl wherein said alkyl is optionally substituted with a carbocyclic or heterocyclic wherein said carbocyclic or heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen, (CH<sub>2</sub>)<sub>n</sub>C(R')R' wherein n is 0 to 4 and each R' is independently selected from the

25

group consisting of hydrido, hydroxy, amino, O, S, and alkyl,  
 $(\text{CH}_2)_n\text{NHCON}(\text{R}')\text{R}'$  wherein n is 0 to 4 and each R' is  
independently selected from the group consisting of hydrido,  
hydroxy, amino, and alkyl,  $(\text{CH}_2)_n\text{NHC}(\text{O})\text{OR}'$  wherein n is 0 to 4  
5 and R' is selected from the group consisting of hydrido, hydroxy,  
amino, and alkyl; alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino,  
aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, halogen,  
acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl,  
hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy,  
10 dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate,  
isothiocyanate, alkylidioxy, hydroxyalkyl, alkylamino,  
alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl,  
alkynyl, dialkylaminoalkyloxy, and heterocyclic wherein said  
heterocyclic is optionally substituted with one to six substituents  
15 selected from the group consisting of alkyl, alkylamino, aminoalkyl,  
hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino,  
dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy,  
alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl,  
heteroaryl wherein said heteroaryl is optionally substituted with one  
20 or more halogen,  $(\text{CH}_2)_n\text{C}(\text{R}')\text{R}'$  wherein n is 0 to 4 and each R' is  
independently selected from the group consisting of hydrido,  
hydroxy, amino, O, S, and alkyl,  $(\text{CH}_2)_n\text{NHCON}(\text{R}')\text{R}'$  wherein n is  
0 to 4 and each R' is independently selected from the group  
consisting of hydrido, hydroxy, amino, and alkyl,  
25  $(\text{CH}_2)_n\text{NHC}(\text{O})\text{OR}'$  wherein n is 0 to 4 and R' is selected from the  
group consisting of hydrido, hydroxy, amino, and alkyl,





$R^{17}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl; and

$R^{18}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

22. The compound of claim 21,

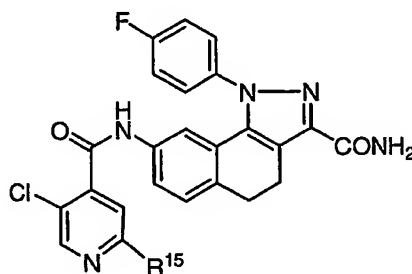
wherein

$R^{16}$  is selected from the group consisting of: hydrido, halogen, and lower alkyl.

23. The compound of claim 22 selected from the group consisting of:

1-(4-Fluorophenyl)-8-[(2-morpholin-4-ylisonicotinoyl)amino]-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide.

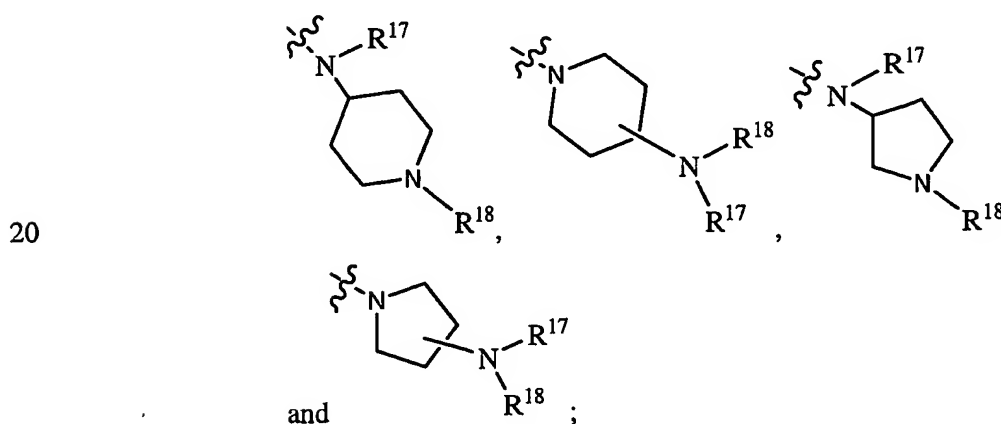
5                    24.    The compound of claim 22 of the Formula



wherein

10                     $R^{15}$  is selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl wherein said alkyl is optionally substituted with a carbocyclic or heterocyclic wherein said carbocyclic or heterocyclic is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, 15                    halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen,  $(CH_2)_n C(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl, 20                     $(CH_2)_n NHCON(R')R'$  wherein n is 0 to 4 and each  $R'$  is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl,  $(CH_2)_n NHC(O)OR'$  wherein n is 0 to 4 and  $R'$  is selected from the group consisting of hydrido, hydroxy, amino, and alkyl; alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, halogen, 25                    acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl,

hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy,  
dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate,  
isothiocyanate, alkylidioxy, hydroxyalkyl, alkylamino,  
alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl,  
5 alkynyl, dialkylaminoalkyloxy, and heterocyclic wherein said  
heterocyclic is optionally substituted with one to six substituents  
selected from the group consisting of alkyl, alkylamino, aminoalkyl,  
hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino,  
dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy,  
10 alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl,  
heteroaryl wherein said heteroaryl is optionally substituted with one  
or more halogen,  $(CH_2)_n C(R')R'$  wherein n is 0 to 4 and each R' is  
independently selected from the group consisting of hydrido,  
hydroxy, amino, O, S, and alkyl,  $(CH_2)_n NHCON(R')R'$  wherein n is  
15 0 to 4 and each R' is independently selected from the group  
consisting of hydrido, hydroxy, amino, and alkyl,  
 $(CH_2)_n NHC(O)OR'$  wherein n is 0 to 4 and R' is selected from the  
group consisting of hydrido, hydroxy, amino, and alkyl,



$R^{17}$  is selected from the group consisting of: alkyl, hydroxyalkyl,  
alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl,  
alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n =  
25 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl,

heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl; and

5  $R^{18}$  is selected from the group consisting of: alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, haloalkyl, acyl, thioalkyl, dialkylaminoacyl, alkylsulfonyl, arylsulfonyl, CO(alkyl), CO(aryl), CO(CH<sub>2</sub>)<sub>n</sub>OH [n = 0 to 4], CO<sub>2</sub>(alkyl), CON(alkyl)(alkyl'), formyl, cycloalkyl, heterocyclic, hydroxyalkoxyalkyl, alkenylalkyl, alkynylalkyl, arylalkyl, and heteroarylalkyl;

10 or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

25. The compound of claim 24 selected from the group consisting of:

15 8-{[2-(Aminomethyl)-5-chloroisonicotinoyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

8-({[3-Chloro-6-(morpholin-4-ylmethyl)pyridin-2-yl]carbonyl}amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

20 8-({[5-Chloro-2-(2-morpholin-4-ylethyl)isonicotinoyl]amino})-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

25 8-({[5-Chloro-2-[2-(dimethylamino)ethyl]isonicotinoyl]amino})-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

8-({[(5-Chloro-2,4'-bipyridin-4-yl)carbonyl]amino})-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

30 8-({[(5-chloro-1'-methyl-1',2',3',6'-tetrahydro-2,4'-bipyridin-4-yl)carbonyl]amino})-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide, and

8-([5-chloro-2-(1,4-diazepan-1-yl)isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide.

5

26. The compound of claim 24 wherein R<sup>15</sup> is piperazine attached at position 1 of the piperazine wherein said piperazine is optionally substituted with one to six substituents selected from the group consisting of alkyl, alkylamino, aminoalkyl, hydroxyalkyl, alkylaminoalkyl, alkylaminoalkylamino, dialkylaminoalkylamino, alkylamino(alkyl)amino, alkoxy, alkoxyalkyl, oxo, hydroxy, amino, halogen, cyano, nitro, acyl, heteroaryl wherein said heteroaryl is optionally substituted with one or more halogen, (CH<sub>2</sub>)<sub>n</sub>C(R')R' wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, O, S, and alkyl, (CH<sub>2</sub>)<sub>n</sub>NHCON(R')R' wherein n is 0 to 4 and each R' is independently selected from the group consisting of hydrido, hydroxy, amino, and alkyl, (CH<sub>2</sub>)<sub>n</sub>NHC(O)OR' wherein n is 0 to 4 and R' is selected from the group consisting of hydrido, hydroxy, amino, and alkyl.

20

27. The compound of claim 26 selected from the group consisting of:

8-([5-Chloro-2-[4-(2-hydroxyethyl)piperazin-1-yl]isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

25

8-([5-Chloro-2-[4-(2-methoxyethyl)piperazin-1-yl]isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

30

8-([5-Chloro-2-{[2-(dimethylamino)ethyl]amino}isonicotinoyl]amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

8-({5-Chloro-2-[(3R)-3-methylpiperazin-1-yl]isonicotinoyl} amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

5 8-({5-Chloro-2-[(3S)-3-methylpiperazin-1-yl]isonicotinoyl} amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

8-({5-Chloro-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]isonicotinoyl} amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

10 8-({5-Chloro-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]isonicotinoyl} amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

15 8-({5-Chloro-2-[(3R)-3,4-dimethylpiperazin-1-yl]isonicotinoyl} amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

8-({5-Chloro-2-[(3S)-3,4-dimethylpiperazin-1-yl]isonicotinoyl} amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

20 8-([5-Chloro-2-(4-ethylpiperazin-1-yl)isonicotinoyl] amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide,

8-([5-Chloro-2-(4-isopropylpiperazin-1-yl)isonicotinoyl] amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide, and

25 8-([5-Chloro-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]carbonyl} amino)-1-(4-fluorophenyl)-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide.

28. A composition comprising the compound of claim 1, 2, 3, 4, 5, 6, 7,  
30 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 and at least one pharmaceutically acceptable carrier.

29. A method of treating cancer, inflammation or an inflammation associated disorder in a subject, said method comprising administering to the subject having or susceptible to such cancer, inflammation or inflammation associated disorder, a therapeutically-effective amount of a compound of claim 1, 2,  
5 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27.

30. The method of claim 29 for use in the treatment of cancer.

10 31. The method of claim 29 for use in the treatment of inflammation.

32. The method of claim 29 for use in the treatment of an inflammation-associated disorder.

15 33. The method of claim 32 wherein the inflammation-associated disorder is arthritis.

34. The method of claim 32 wherein the inflammation-associated disorder is pain.

20 35. The method of claim 32 wherein the inflammation-associated disorder is fever.

## INTERNATIONAL SEARCH REPORT

PCT/US 03/08917

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/54 A61K31/416 A61P29/00 C07D401/12 C07D413/12  
 C07D403/12 C07D409/14 C07D417/12 C07D409/12 C07D405/14  
 C07D405/12 C07D405/10 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 760 068 A (GRANETO MATTHEW J ET AL) 2 June 1998 (1998-06-02) column 4, line 30 - line 67; claims 6-8; table IX	1,29
A	HAMILTON R W: "The antiarrhythmic and antiinflammatory activity of a series of tricyclic pyrazoles" JOURNAL OF HETEROCYCLIC CHEMISTRY, PROVO, UT, US, vol. 13, no. 3, 1 June 1976 (1976-06-01), pages 545-553, XP002085959 ISSN: 0022-152X compounds 79-83,86-88,91 page 546; table V	1,29

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

9 July 2003

Date of mailing of the international search report

29/07/2003

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Authorized officer

De Jong, B



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/08917

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 29-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

PCT/US 03/08917

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